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Errata

In the next preceding issue (New York Number), page 670, the last sentence of the third paragraph, giving the dose of digitaline nativelle, should read "We begin with 0.05 mg. once or twice daily, increasing the dosage to 0.1 mg. daily."

On the same page, seventh paragraph, the first sentence should read "If the hypertension persists (Hochdruckstaung—high blood pressure due to pulmonary stasis) more active digitalization is necessary, the drug being given in doses of 0.1 to 0.2 mg. daily."

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THE MEDICAL CLINICS of NORTH AMERICA

Vol-30

1946

CHICAGO NUMBER

SYMPOSIUM ON PEDIATRICS

FOREWORD

PEDIATRIC centers throughout the country have been flooded with requests from service men for further training in pediatrics. Some whose program was interrupted wish to complete their requirements for eligibility to the American Board of Pediatrics. Some wish to begin now the two years of special training which they had had in mind before they were called into active service. Others wish short refresher courses or periods of observation in hospital or clinic to give them again the "feel" of the pediatric approach, and to familiarize themselves with the recent advances in diagnosis and treatment which have come about during their enforced absence from their chosen field. Although every effort is being made to meet this need, there may be some who will be disappointed. There is, however, one type of refresher course which is open to all. That is the printed page. It is my hope that the discussions of current pediatric problems appearing in this volume will prove of interest to veterans and to all others who are devoting themselves in some degree to the medical care of children.

It was with no little misgiving that I undertook the sponsorship of this number of the *Medical Clinics of North America*. It seemed unlikely that the physicians on the home front, long wearied by the excessive demands which have been placed upon them, would undertake an additional burden. It is indeed gratifying to report that every single one approached volunteered his services and that only a very few—due to unforeseen circumstances, were unable to complete their assignment. To my colleagues who have responded so generously, I wish to express my sincerest thanks and warmest appreciation.

STANLEY GIBSON, M.D.

THE GROWTH OF PEDIATRICS IN THE CHICAGO AREA

ISAAC A. ABT, M D, D Sc.*

IN view of the fact that this is a pediatric number of the *Medical Clinics of North America* contributed by the pediatricians of Chicago, it may not be inappropriate to sketch briefly the growth of pediatrics in this area. I am sure that neither my Chicago colleagues nor the writer would wish to be boastful of the accomplishments of the past, but nevertheless it is interesting to take note of the road which we have traveled from the beginning, at least until that period when pediatrics was established on firm ground.

BEGINNINGS OF PEDIATRICS AS A SPECIALTY

Pediatrics is one of the youngest of the special branches of medicine. Before the middle of the nineteenth century children's hospitals had hardly been organized in this country and children's specialists were practically unknown except in a few isolated instances where they acted as teachers and specialists to a limited extent. Perhaps none of the so-called specialists of the early period restricted their practice to sick children and most of them combined pediatrics with general medicine or obstetrics.

It may be said that the development of pediatrics in the Chicago area began at the time when special hospital wards or pavilions were first established for the treatment of children and when special instruction in this branch of medicine was introduced into the medical curriculum. The first mention of instruction in diseases of children in Chicago is found in the published announcement that *M. L. Knapp* was professor of obstetrics and the diseases of women and children at Rush Medical College about 1843. *Edward Oscar Fitzland Roler* (1833-1907) became professor of diseases of women and children at the Chicago Medical College (now Northwestern University Medical School). He conformed to the prevailing custom of the day by stressing instruction in obstetrics and teaching the diseases of infancy and childhood by delivering a few general lectures. *Charles Gilman Smith* accepted the professorship of diseases of children at the Women's Medical College in 1870, a position he held for several years, he enjoyed the distinction of having a very extensive general practice, was considered a resourceful man in diagnosis and therapy and had an affable personality.

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Chicago

The Foundlings Home of Chicago was established in 1871 and was conducted by *George Elias Shipman*, a homeopathic physician. He was one of the early practitioners who devoted considerable attention to diseases of infants and children.

At Rush Medical College, *James Suydan Knox* was appointed lecturer in obstetrics in 1873, adjunct professor of obstetrics and diseases of children in 1882, and full professor of obstetrics and diseases of children in 1888. Like his contemporaries, he devoted very little time to teaching diseases of children.

Courses of instruction in pediatrics were established at the various medical schools in Chicago from 1880 to 1890. *Marcus P. Hatfield* (1849-1909) had prepared himself in the clinical study of the diseases of infancy and childhood under the pioneer and master, *Edward Henoeh of Berlin*. Hatfield was appointed head of the newly organized department of diseases of children at the old Chicago Medical College, now Northwestern University. He served in that capacity from 1881 until 1896. He delivered lectures and held a weekly clinic in the amphitheater of the medical school, where he demonstrated the ambulatory material that was available from the outpatient department.

Before assuming the position in pediatrics Hatfield had taught organic chemistry, as well as inorganic chemistry and toxicology. He contributed the article on Scarlet Fever for Starr's "American Text-book of Diseases of Children" (1898), in which he gave a historical account of the disease, describing a seventeenth century epidemic. He surmised that the disease was of bacterial origin, though no definite knowledge on this point had been discovered. He gave a good clinical description of the illness and noted that nephritis was the most dreaded of all complications.

Hatfield also contributed an article to Keating's "Cyclopedia of Diseases of Children" (1890) entitled "Contractions of the Liver Cirrhosis (Atrophic and Hypertrophic), Acute Yellow Atrophy and Ascites." He conceded that cirrhosis of the liver was extremely rare in children, though he noted that the condition is frequently associated with congenital syphilis, also that malaria is a not-infrequent cause in the regions where the disease is endemic.

Hatfield also read an interesting paper before the American Pediatric Society in 1889 on two fatal cases of biliary cirrhosis, with the subtitle "Congenital Pernicious Icterus in the Same Family." The first baby died of intense icterus on the fourth day and the second baby of icterus and convulsions on the thirteenth day of life. Today we would classify these cases as familial icterus gravis or erythroblastosis fetalis. The mothers, we would say today, would be Rh-negative, while the affected child and father would be Rh-positive. It is interesting to note that this clinical condition occurred that early, and received attention of the physicians of the period.

Hatfield also was the author of "Practical Urinalysis," "Compend of Diseases of Children" and "Acute Contagious Diseases of Childhood" While he was at the Chicago Medical College his associates were *J C Cook* and *C A Storey*

In reviewing the records of pediatric teachers in Chicago, it is evident that Hatfield was the first professor of pediatrics in any of the Chicago medical schools, though *Frank E Waxham*, one of the founders of the College of Physicians and Surgeons (now the medical school of the University of Illinois), received the appointment as professor of diseases of children in 1882 Waxham was one of the first to perform O'Dwyer's operation of intubation in Chicago in 1885 He wrote papers on this subject and acquired considerable skill in the operation. It is interesting to note that his recourse to intubation aroused violent opposition, not only from laymen, who threatened his life, but also from some of his colleagues Later his procedure was approved O'Dwyer wrote to him that he did not know which to admire more, Waxham's technical skill or his courage in facing and overcoming opposition.

Waxham wrote papers on intubation, diphtheria, antitoxin tuberculosis and tumors of the larynx He also contributed the article on "Measles" for Keating's "Cyclopedia" Waxham was also interested in laryngology and rhinology and taught this branch, first in Chicago and later at the University of Colorado

In 1892 the College of Physicians and Surgeons appointed *Walter S Christopher* to succeed Frank E. Waxham as professor of diseases of children Christopher was very popular as a practitioner and enjoyed an excellent reputation as a teacher After graduation from the Medical College of Ohio in 1883, he interned at Cincinnati General Hospital and was appointed demonstrator of chemistry at the same medical school At the same time, he was consulting chemist for the Rockford Pottery Company, where he made some important discoveries in perfecting the glazes for the pottery ware He taught internal medicine at the University of Michigan and then came to Chicago, where he taught pediatrics at the Chicago Polyclinic and also at the Chicago College of Physicians and Surgeons

Christopher was a colorful personality, and with the imaginative mind of a scientist, he propounded hypotheses which stimulated investigation He proposed his so-called "safranin test," which he thought was reliable for the detection of abnormal glucose in the urine He also conceived the thought that a positive safranin test indicated certain forms of autotoxemia

He was interested in civic affairs and was appointed a member of the Chicago Board of Education Christopher, in association with *Fred W Smedley* (the latter connected with the Department of Education at the University of Chicago), made a report on Child Study to the Board They investigated the relationship between physical

condition and intellectual capacity, also, using the Ergograph, they studied fatigue among school children, and a number of similar problems that related to the physical condition of the child in connection with his school work. They likewise pointed out that the mental training of the child should be adjusted to his health and strength.

Christopher published a monograph on "Summer Complaint and Infant Feeding" which was in accord with the thought of the time. In considering the treatment of summer complaint, he preferred calomel as a preliminary cathartic. He gave a six months old child 1 grain every four hours until it had taken three doses. He thought it was not possible to give too large a dose because the excess was swept out of the bowel. The doctors of that generation believed in the cleaning-out process. We can only remember this kind of treatment with sadness.

In his address as Chairman of the Section on Diseases of Children of the American Medical Association in 1894, Christopher discussed "Pediatrics as a Specialty." He pointed out that the study of pediatrics encompassed only a portion of the life cycle but, in contradistinction to so-called medical specialties, pediatrics considered the total individual, his ailments, his growth and his development. In his presidential address before the American Pediatric Society in 1902 his theme was "Development the Keynote of Pediatrics."

He contributed an article on bronchitis to Starr's "American Textbook of Children's Diseases," pointing out that bronchitis frequently masked typhoid fever, though under some circumstances it might be a manifestation of tuberculous infection. He also thought there might be a causal relationship between rickets and bronchitis.

Christopher died at the early age of 46. He led a life of great activity and incessant toil, and left a lasting impression on pediatrics in Chicago. Perhaps he, more than anyone else before him, taught the public what apparently they had not known before, that trained pediatricians could be of very special service in the care of infants and children.

Upon the death of J. Suydan Knox in 1892, pediatrics was separated from the department of obstetrics at Rush Medical College and *Alfred Cleveland Cotton* was appointed to the chair of pediatrics, also becoming attending pediatrician to the Presbyterian Hospital. He wrote a treatise on anatomy, physiology and hygiene of the developmental period, and also was a frequent contributor to the literature. In 1901 he reported on diabetes mellitus in children, this was before the insulin treatment had been discovered and the disease was involved in obscurity, with a fatal termination in a short time. Cotton advised opium in the vain hope of retarding the progress of the disease, this was the customary treatment. He also used alkalis to counteract acidosis. Strict dietetic treatment was insisted upon and carbohydrates were restricted rigidly.

In 1904 he described an epidemic of vulvovaginitis among children before the American Pediatric Society. Koplik in New York had read a paper the year previously on the prophylactic measures against the spread of the disease in children's hospitals. He referred to an epidemic in which nineteen cases occurred in a year, in a total of 319 patients (6 per cent of all patients admitted). The children ranged from six months to thirteen years of age. The average duration of the disease was 116 days, though in one child, including remissions, the duration was 252 days. The patients were pronounced cured if repeated negative smears were obtained nine days after cessation of treatment.

Cotton was a picturesque figure—tall and erect, with long, white locks. He exerted a telling influence on pediatrics in the Midwest when it was in its formative period. He taught large classes of undergraduates, contacted many interns in the hospitals and was unusually popular with his colleagues, as well as in the medical organizations throughout the state. Among his corps of instructors and assistants may be mentioned *Julia Merrill*, *W. J. Butler*, *J. W. Vandersluice*, *Frank S. Churchill*, *Charles A. Wade* and *Frank W. Allin*.

Another pioneer and striking personality was *Charles Warrington Earle*, a veteran of the Civil War. He volunteered at the age of 16, and was wounded and sent to Libby Prison, from which he finally escaped. He graduated from the Chicago Medical College, now Northwestern University, in 1870. He was one of the organizers of the Women's Medical College and of the College of Physicians and Surgeons, where he was at first professor of obstetrics, later becoming professor of diseases of children at the Women's Medical College.

Earle wrote many interesting case reports, contributed to Keating's "Cyclopedia," an article on acute and chronic constipation, and to Starr's "American Textbook of Diseases of Children," a chapter on epidemic influenza.

The librarian of the University of Illinois College of Medicine kindly furnished the writer a bound copy of Earle's reprints which were published from 1881 to 1893. He dealt with a great variety of subjects. To show the wide range of his interests I will cite a few of the titles: *Etiology and Treatment of Inebriety* (1881), *Antiseptic Obstetrics* (1888), *Infant Feeding* (1888), *Influence of Sewerage and Water Pollution on the Prevalence and Severity of Diphtheria* (1888), *Progress in the Study and Practice of Medicine by Women* (1891), *The Paralysis of Diphtheria* (1891), *Typhoid Fever in Infancy and Childhood* (1892), *Present Status of the Etiology of Whooping Cough and Its Treatment with Bromoform* (1893).

The present writer was particularly interested in Earle's views on water pollution by sewerage and its influence on diphtheria. Earle quoted another physician who was a strong believer in the specific cause of diphtheria, discounting the sewer gas theory and flatly

stating "no germs, no diphtheria." Earle himself thought that there was such a mass of evidence in favor of the germ theory of diphtheria that belief in it was almost irresistible. He concluded that sewers and sewer gas had nothing to do with the etiology of the disease. It will be remembered that this paper was written in 1888 and the diphtheria organism had been discovered by Klebs and Löffler in 1883-84.

In his doctorate address before the Women's Medical School Earle justified women in the study of medicine. He championed their cause and encouraged them to make a place for themselves in medical practice.

Earle read a paper on typhoid fever in infancy before a meeting of the American Pediatric Society in 1892. At this time William Perry Northrup of New York maintained that in 2000 autopsies at the New York Infant Asylum he had never seen typhoid fever in an infant under two years. This pronouncement of Northrup became a prevailing dogma at this time. Earle contested this opinion by saying there was no reason why infants should not have typhoid fever, because the source of infection might be present not only in the milk and water which they drank but in the atmosphere which they breathed. Earle reported a series of twenty-one cases occurring in the city of Chicago during the previous year and a half. The youngest of his patients was 5 months and 4 days old, the oldest were between 10 and 15. At the time this paper was written the sewage from the city was still for the most part emptying into the lake, which constituted the city's water supply. Facilities for laboratory diagnosis were nonexistent. Earle stated that he suspected the disease when the young patient suffered from headache, apathy, fever (most marked at night), gastrointestinal disturbances, enlarged spleen, and rose spots.

At the same meeting Christopher presented a paper in which he said he had encountered cases in infancy which seemed to justify the diagnosis of typhoid fever. One notes today that this diagnosis may be confirmed by laboratory methods. The strongest point in the clinical diagnosis of the early period was the discovery of the rose spots.

Abraham Jacobi, in participating in the discussion, said he had seen the disease in infants under two years and that the diagnosis in most cases was made by exclusion. In 1892 it was not yet possible to recover the organisms from the blood, the urine and stools, the Widal test had not yet been discovered, and the significance of leukopenia had not been determined.

It is worthy of note that Charles Warrington Earle was not a pediatrician in the modern sense, though he was extremely interested in this branch of medicine. Like most men of his period he was engaged in general practice, which included obstetrics and office gynecology, as well as internal medicine. He represented the family physician of the period.

Somewhat later, though still to be considered a pioneer, should be

mentioned the name of *John M. Dodson* (1859-1933). He first taught pediatrics at Northwestern University Women's Medical College from 1894 to 1897 and was appointed professor of pediatrics at Rush Medical College in 1899. He was a man of sterling qualities. He was keenly interested in the administrative department of medicine, for many years he was Dean at Rush Medical College, where he was a friend and adviser of students. His inspiration, direction and friendship toward all can never be adequately described.

In association with Richard E. Schmidt, architect, Dodson wrote a very thoughtful paper in the writer's "System of Pediatrics" on hospital building and management as related to infants and children. Scanning these pages, one finds ground plans and specifications for many of the children's hospitals which had been built at that time, and also numerous suggestions on hospital administration, hospital accounting, hospital equipment, construction of cubicles, wards and private rooms, heating, insulation and ventilation, indeed all of the details of building and management which the minds of the architect and medical man could reasonably conceive.

DEVELOPMENT OF HOSPITALS FOR CHILDREN

With an increased interest in the study of the diseases of infants and children in this area, a necessity arose for the construction of children's hospitals and wards. The first hospital of this kind was founded as early as 1865 and was known as the *Chicago Hospital for Women and Children*. This institution was later named in honor of its founder, the Mary Thompson Hospital, though it is now known again as the Women's and Children's Hospital. The first announcement of the hospital stated that it was to be devoted to the care of women and children of the respectable poor. It accommodated fourteen patients and was intended chiefly for the widows and orphans of the soldiers of the Civil War.

The *Cook County Hospital*, organized in 1847, occupied various quarters until the present site at Harrison and Wood Streets was selected in 1874. The Children's Ward, known as Ward 13, was established in the hospital about 1885. The main floor of the ward accommodated the older children, while a sort of balcony or mezzanine floor was reserved for the infants. This section was not particularly well adapted for their welfare or their hygienic care. The ventilation was poor, cross infections were a common occurrence and the management of the ward was strikingly defective. No special precautions were taken to prevent house infections or for securing the proper milk supply, or for its preparation for infant use. The writer can personally bear witness to the fact that the infant mortality in this ward was discouragingly high. During the summer time conditions in the infants department were particularly bad. In many instances the little patients were admitted in a condition which we designated as

marasmus associated with diarrhea. Most frequently a terminal pneumonia ended the scene

In the early years of Cook County Hospital the appointment of attending physicians to the institution was made on the basis of political preferment. It is obvious that this method of selecting an attending staff was far from being an ideal system, to correct the political abuses involved, the State legislature in 1905 passed an enactment making it compulsory for all attending physicians seeking positions on the staff to submit to a civil service examination. The first pediatric staff was selected in conformity with this new law about 1905. The members of the newly selected staff were *William J. Butler*, *Frank S. Churchill*, *Gottfried Koehler* and *Isaac A. Abt*. The interns served for about three weeks. During this short period they did not learn much for themselves, nor were they of any great help to the sick infants.

The *Children's Memorial Hospital of Chicago* was founded in 1884 by Mrs. Julia F. Porter in memory of her son. Originally it bore the name, "The Morris Porter Memorial Hospital for Children," and it accommodated thirty patients. In 1903 the hospital was rebuilt and reorganized, and the name was changed to "The Children's Memorial Hospital." Several pavilions have been erected since that date, and the hospital now has a capacity of 265 beds and a large outpatient department. It also accommodates private patients in the Martha Wilson Pavilion.

It has already been stated that Walter S. Christopher was one of the early attending physicians to this hospital. Somewhat later *Samuel Walker*, *George Baxter* and *Frank Spooner Churchill* were also attending physicians.

Churchill wrote on a variety of clinical subjects, such as acute leukemia in early life and the wetnurse in hospital practice. In the latter paper he recommended that a baby seriously ill should receive at least one-half breast milk throughout the period of the critical illness. In 1909 he made a report on the medical work of the Juvenile Court of Cook County. He found the incidence of gonorrheal infection among girls very high. In 1898 he also reported on examinations of the urine of normal infants and children, he studied the amount secreted, specific gravity, urea, and presence of albumin and sugar, as well as chloride and phosphate. He found the amount secreted small and the specific gravity high. In 1912 he made serological tests for syphilis among the children at the institution. He found thirty-eight positive reactions, with twenty-eight Wassermann and eighty-three Noguchi tests. His percentage of positive reactions was very high, in the light of our modern investigations, and may have been due to errors in interpretation, or as Mathias Nicoll of New York said at the time, to the Noguchi test being "too sensitive for clinical use."

Henry F. Helmholtz was attending physician and later medical

director of the Children's Memorial Hospital till 1920. In association with Samuel Amberg he was active in the conduct of the Otto S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital. Helmholtz collaborated with Amberg in studies on pyelitis and diseases of the genito-urinary system in infancy and childhood.

Joseph Brennemann succeeded Helmholtz as chief of staff at the Children's Memorial Hospital. Brennemann was intensely interested and absorbed in pediatrics. He was very popular with his colleagues and beloved and respected by his interns and students. He had a reflective and philosophic mode of thinking which showed itself in his spoken and in his written word.

He wrote numerous papers and edited Brennemann's "Practice of Pediatrics," which is a compendium contributed by numerous authors. One of his early publications was entitled, "A Contribution to Our Knowledge of the Etiology and Nature of Hard Curds of Infant Stools." He referred to this paper, attempting anonymity, in a reminiscent essay before the American Pediatric Society in 1938, saying in his modest way "From an obscure source, in the Middle West, came reports in 1911 and 1913 which demonstrated that even larger and harder curds were formed when fat-free milk was fed instead of whole milk, that hard curds could be produced and made to disappear by alternating raw and boiled milk feedings in a susceptible baby, and that these curds grew larger in the stomach for around two hours, and harder and more impermeable the longer they existed anywhere."

He contributed a paper on infant feeding to Abt's Pediatrics and wrote, to mention only a few titles, on psychologic aspects of nutrition in childhood, the menace of psychiatry, the human side of the hospital, abdominal pain, incidence and significance of rheumatic nodules in children, and several papers in Brennemann's system. Brennemann died in July, 1944, aged 72.

The *Durand Hospital for Acute Communicable Diseases* was erected in 1912, founded by Harold and Edith McCormick as a memorial to their son who died of scarlet fever. Many important investigations were conducted on communicable diseases under the supervision of the members of the John McCormick Institute. Unfortunately, the Durand Hospital closed after the depression of 1930.

Ludwig Hektoen was the moving spirit of the scientific activities of the hospital. *George* and *Gladys Dick* conducted most of their investigations of scarlet fever here and *George H. Weaver* was the clinical mainstay of the organization. Weaver wrote on scarlet fever in the writer's System of Pediatrics and the paper shows very careful consideration of the disease, based on keen observation, extensive experience and fine clinical judgment. Other active attending physicians at Durand were *Alice Hamilton* and *George Ruediger*.

The *Children's Department of Michael Reese Hospital* was organized in 1890 as a small ward with twelve beds. *Ernst Lackner* and

Frank Cary were the first attending physicians. In 1894 a building was erected on the property of the hospital, accommodating fifty children. Lackner remained and the writer succeeded Cary.

The new *Sarah Morris Children's Pavilion*, built across the street from the hospital in 1912, accommodates about 125 patients and also contains about twenty private rooms. The writer was active in the organization of the *Sarah Morris*, was attending physician at Cook County Hospital, taught pediatrics at Rush Medical College, and headed the department at Northwestern, published a *System of Pediatrics*, edited the *Yearbook of Pediatrics* for over forty years, and wrote numerous clinical papers which will not be enumerated for fear of prolixity.

NOTABLE CONTRIBUTORS TO PEDIATRIC LITERATURE

There have been many notable contributions to the pediatric literature from this area, indeed, they are too numerous to mention within the limits of the space allowed, but the writer can not forego reference to the contributions of *Oscar T. Schultz*, who was formerly pathologist at Michael Reese Hospital. His papers written for the writer's *System* on the pathology of the lungs and the kidneys are outstanding, and present an extensive review of the subjects. They merit the reading study of all who are interested in these subjects. Schultz's contribution on the tumors of childhood, also in the writer's *System*, is a very significant presentation. Perhaps nowhere else in medical literature will one find such an extensive and exhaustive review of the subject. He presents a description of tumors of various organs and organ systems. He considers neoplasms of every period of life from the newborn to adolescence. The vast amount of literature consulted and cited represents the most diligent and careful research. Indeed, one may say that Schultz's presentation of tumors in childhood is a classic in medical literature.

Another chapter in the writer's *System* which merits attention and commendation is on "Hygiene of the School Age" by *Josephine E. Young*. Dr. Young at the time of writing this treatise was medical inspector of the Chicago Public Schools, school physician in the School of Education, University of Chicago, and assistant professor of neurology at Rush Medical College. She discussed almost every conceivable point concerning hygiene of the school age. She inquired into the problems of school ventilation, heating, lighting, sanitation, protection against infection, and all factors relating to school health and physical education. She also discussed the education of parents, and her section on mental hygiene is a model of thoroughness and simplicity. In this paper Dr. Young made a notable contribution which will be regarded as outstanding by those who refer to it.

The writer also wishes to pay tribute to the contribution which *Richard Herman Jaffe* made to the students and practitioners of pedi-

atrics in this area during the latter years of his life. He died in 1937 at the early age of 49. Jaffe was director of the laboratories of Cook County Hospital. He was trained in the famous pathological school of Vienna and accumulated a vast experience and knowledge of his subject. Jaffe was a genial soul and a master in the art of teaching.

Maurice L. Blatt, who was chief of staff of the pediatric department of Cook County Hospital, and who was a most efficient administrator, used his influence with Dr. Jaffe to give a series of pathological demonstrations on pediatric material. These conferences were held once a month throughout the school year. His collection and his presentation of the material were complete and excellent. Each session was not only instructive but stimulating. Nothing could have been of greater value from an educational standpoint to practitioners and students alike. These demonstrations marked a memorable epoch in pediatric training in Chicago.

MODERN PROGRESS

With the beginning of the twentieth century, pediatrics was recognized as an established branch of medicine. Undergraduate instruction in medical schools has shown marked improvement in methods of teaching and presentation of subject, and planning of the curriculum. If one pauses to compare the first pediatricians with those of later days, it is obvious that the earlier workers were limited by lack of diagnostic resources, their studies and reports were altogether of a clinical nature and their therapy was empirical and in most cases useless.

Since those early clinical days we have traveled a long distance. Biological chemistry has provided new methods and refined techniques. Advances in physiology have helped to explain the energy metabolism in health and disease, and in comparatively recent times studies in immunity and allergy have not only been of theoretical but great practical interest in the prevention of disease.

The development of bacteriology has been of the greatest importance in the recognition of diseases of bacterial origin. Earle and Christopher had difficulty in proving their diagnoses of typhoid fever because they had no technic of recovering the organisms from the blood or excreta of the body. The places that vitamins and the x-ray have taken in modern medical thought are so well known that they require no discussion at this point.

But to one who has practiced medicine a number of decades and who projects himself backwards to the beginning of his medical career, the whole panorama seems to have moved so swiftly that one apparently is lost in the maze. Medical theory reverses itself from period to period. The humoral theory held sway for twenty centuries. It was the product of speculative thought and the phantasies of abstract philosophy. In the middle of the eighteenth century when

Virchow postulated his theories of cellular pathology, the cell was all-important and humoral pathology was banished and tabooed. It was at this time that clinical methods of examination came into their ascendancy. It was the practice of that day to think in terms of morbid anatomy and the relationship between disease and tissue changes.

Meanwhile, Cohnheim had discovered the nature of inflammation and diapedesis, shedding further light on medical as well as surgical problems. In some ways succeeding discoveries altered the validity of the cellular pathology of Virchow, but physicians were at that time, as they are now, thinking in terms of the relationship of morbid anatomy to disease processes. At the same time, innovations in the knowledge of physiology and chemistry have changed considerably the medical man's conception of disease processes.

Now humoral pathology has in a modern sense been revived, due to brilliant investigations in chemistry and physiology, and its rebirth has signalized medical progress in many directions. Yet to us oldsters it is a strange language. The neomedic is undoubtedly well trained in the structural changes of tissues and organs, yet he is intensively thinking of disease in terms of changes in body fluids. The young doctor and the old doctor, meeting as they do, no longer think or talk alike. The elder still tries to make a diagnosis from a clinical examination, to compare the possible clinical findings with the pathological changes, and to defer the punctures and the tests of fluids, as well as the x-ray, for corroborative proof. The younger man is quick to make the laboratory tests, to examine the fluids and the secretions, to tap here and there. He thinks differently, perhaps more wisely, but it is difficult for the old man to understand him. In discussing disease of an organ, for example the heart, he does not think so much of dilatation or degeneration or pathological adhesions, but he is more interested in the mechanism of oxidation of the cells and the respiration of muscles, the enzyme chemistry and the relationship between oxygen and lactic acid in muscular metabolism.


But progress takes this pathway. New facts are sometimes difficult to learn, sometimes more difficult to employ rationally. In any event, it seems to the writer that it is not well to forget the old and tested facts, while learning the new.

To return to our subject, pediatrics in the Chicago area has made vast strides since the writer began to practice—in fact, so vast and so rapid has been its development that one is almost frightened by the amount of new data which have been accumulated and the new methods which are being practiced. However, it should not be forgotten that the early clinicians who laid the groundwork made the future of pediatrics possible.

The pediatricians in the Chicago area have done and are doing their part. If the clinicians and investigators in Chicago have contributed even in small part to the advancement of knowledge and to the safer

and more reliable methods of diagnosis and treatment, they will have benefited in no small degree the health and happiness of our children.

The writer wishes to acknowledge the great debt which pediatrics owes to the younger men who have contributed so much to the development of pediatrics in this area. It is obvious that he could not in justice mention them all by name and give them the credit they deserve. He has therefore decided to omit the names of all contemporary and active workers in this field. Credit and acclaim for their labor will be awarded by the historian of the future.



SKIN CONDITIONS IN THE NEWBORN

A H PARMELEE, M D *

ANY physician whose duties are concerned with the care of the newborn will frequently be faced with conditions of the skin about which he should be familiar in order to give proper advice and treatment.

The skin of the newborn is exquisitely soft and velvety at birth, it is likewise very tender. This is understandable when you remember that up to the moment of his birth he has been living in a veritable water bath and nothing else has touched his skin until now. The necessary handling of the baby at his birth and afterwards subjects this tender skin to traumatic insults of varying degree even in the best of hands and under the best of conditions. The sheets, towels and clothing must be like sandpaper to his tender skin even though they seem soft and smooth to you. These facts should always be kept in mind because it is due to them that the skin constitutes a real potential hazard to the newborn.

Within a few hours after birth there is usually a marked erythema of the entire skin surface giving it the so-called "boiled lobster" appearance. Gradually during the next twenty-four hours the redness fades and gives way to a varying amount of desquamation. This may occur in fine flaky or branlike scales or in larger plaquelike scales which come off in large thin pieces as if the baby were "shedding his skin." This is particularly the case on the trunk and is more noticeable in the skin folds and creases. In some cases the entire body is covered with dry scales even including the palms and soles.

IMPETIGO OF THE NEWBORN

The skin condition which gives rise to most concern in the maternity nursery is the one generally spoken of as impetigo or pemphigus neonatorum. It results from an infection of the skin and might better be called pyoderma or pustulosis neonatorum since the lesions are pustules and do not truly resemble impetigo as we know it in its occurrence on older children and adults.

The organism usually found on culture is a staphylococcus although sometimes a streptococcus has also been isolated. Whether or not these pyogenic organisms are actually causative or are secondary invaders is still not proved. Cultures made of material aspirated from

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isolated pustules are frequently sterile. However that may be, it is quite certain that the condition does at times become epidemic in a nursery and this constitutes strong evidence of its bacterial origin.

The disease starts with the appearance of a few isolated superficial vesicles or blebs which soon become pustular. The pustules rupture spontaneously often within a few hours and leave a red denuded base, but usually no crusts. The lesions may appear on any part of the body, but are most often found in the diaper area, particularly in the groin and on the lower abdomen, and also in the folds of the neck and in the axilla. There are seldom any constitutional symptoms.

The prognosis is almost invariably good, although some cases have been known to develop a fatal generalized sepsis presumably from the infection of the skin. Also it is well to remember that cases of dermatitis exfoliativa neonatorum (Ritter's disease) which probably is an extreme form of impetigo neonatorum, are almost always found where impetigo has been epidemic.

The pathology is characteristically a superficial dermatitis producing vesicles, blebs and pustules. The reason for this reaction of the skin is largely a physiologic peculiarity of the skin of the newborn. The epidermis is loosely attached to the dermis thus permitting epidermolysis to occur with greater ease than is the case in later life. Thus an infection of the skin which in later childhood would cause furuncles and skin abscesses, will in the newborn produce superficial vesicles, blebs and pustules or even extensive epidermolysis with a denuding of very large areas.

The treatment is primarily prophylactic. The skin must be protected from injury and from contamination with infectious organisms. In recent years we have employed a technic suggested by Sanford's experiments at the Presbyterian Hospital. After the baby's birth the face and scalp are gently cleansed of the gross blood and mucus to make him presentable but no other cleansing or bathing is done. No baths of any sort are given during the entire time the infant is in the hospital except that mineral oil is used for cleansing the buttocks when the diaper is changed, and sometimes used in the folds of the neck, groin and axilla if evidences of irritation appear. Since the institution of this technic seven years ago we have had only an occasional case of pustulosis and no epidemics in a yearly census of newborns that runs over five thousand.

The value of this nursery technic lies in the great reduction of the hazards of trauma to the skin due to the minimal amount of handling of the infant, and coincidentally the greatly reduced chance of bacterial contamination.

Strict adherence to rules of asepsis in all nursery procedures is, of course, of greatest importance. This applies not only to the nursing personnel but to the doctors as well. The rules formulated for the nursery must be strictly adhered to by all who enter the nursery or

who handle the infants for any purpose. Respiratory infections, infections on the hands or for that matter any illness on the part of a nurse, a nursery maid, or a doctor should automatically exclude them from the nursery. The attending staff of every hospital with an obstetrical department and a maternity nursery should appoint a chief of the department with full authority to make rules for the conduct of the department and the power to enforce them. If there is a pediatrician on the staff he might be selected to establish the rules and outline the technic for the nursery. But whatever arrangement is made there should be full compliance by all members of the staff. This has long been the practice in larger hospitals, but in many smaller hospitals the conduct of the maternity nursery is often quite haphazard.

In the efficient conduct of a nursery it is also of utmost importance that a head nurse be in charge who has had training and experience in the care of the newborn, and that she have full authority over the nursing personnel in the nursery. A serious handicap to the maintenance of strict asepsis in the nurseries of the smaller hospitals is the practice of calling in relief nurses from other parts of the hospital at certain periods of the day. When this is unavoidable as it conceivably might be in some hospitals, great care should be taken that relief nurses be selected who are not working with infective patients.

The active treatment varies with the clinical experience of the physician. Certainly the infant should be isolated from the unaffected newborns. It is the practice of most physicians to prescribe some antiseptic wash or ointment. Since the vast majority recover in a few days regardless of the treatment used there is no particular reason for engaging in a discussion of the relative merits of the various procedures used. Some of the more commonly prescribed are weak solutions of bichloride of mercury, potassium permanganate or sodium sulfathiazole as a wash. Gentian violet is used as a local application by some. Many prescribe a 2 or 3 per cent ammoniated mercury ointment, or a 5 per cent sulfathiazole ointment or cream. Irradiation with ultraviolet is said by some to have value. There are physicians who advocate breaking open the individual vesicles and pustules as they appear and applying 50 per cent alcohol or some other antiseptic to the denuded underlying skin. In my opinion this is an unnecessary and even meddlesome procedure and it can be dangerous.

Congenital Pustules—While on the subject of impetigo it should be mentioned that now and then infants are born with isolated pustules here and there on various parts of the body. We see about six or eight such cases a year here at Cook County Hospital. Seldom do any new pustules develop later on these infants. After a few days the original pustule or pustules will disappear and that is the end of it. On several occasions we have aspirated the contents of one of these pustules and in every one of our cases thus studied the cultures have been sterile. However, Reed has reported finding hemolytic streptococci in a case

that he studied. The etiology of these lesions is not clear. They certainly are not usually infectious, and may be due to some nonbacterial irritant.

TOXIC ERYTHEMA OF THE NEWBORN

There is a very common and entirely benign skin condition known as toxic erythema. It is characterized by the appearance of small isolated areas of erythema varying in diameter from a few millimeters to 1 or 2 centimeters. In the center of the erythematous patch there is a small whitish or yellowish-white wheal slightly raised from the surface of the skin. The whole lesion so closely resembles a flea bite that we in the nursery in this hospital always speak of the condition as "flea-bite dermatitis." The lesions may be very few in number or quite numerous and sometimes are closely packed together in a given area. They may appear on any part of the body, but are more commonly seen in the diaper area and on the back. The earliest lesions will often make their appearance before the end of the first twenty-four hours. The individual lesions disappear after a few hours but new ones show up in successive crops for several days, in some instances even up to the time the infant leaves the hospital at seven to ten days.

These infants show no signs of illness and their progress is like that of any other infant. No treatment is necessary.

The etiology is not clear. Since the lesions are urticarial in appearance it has been suggested that they are allergic manifestations, perhaps due to a reagin absorbed from the digestive tract, but no proof of this theory is at hand. It has also been suggested that the condition is one of the "pregnancy reactions," that is, due to some hormone transferred to the infant through the placenta or later given directly in the breast milk. Trauma to the skin is quite likely a factor since the distribution of the lesions corresponds to the areas of the skin surface where pressure and irritation are most marked, as for example the diaper area, the back, the shoulders and similar areas.

SCLERODERMA (TRAUMATIC SUBCUTANEOUS FAT NECROSIS)

Quite often we see conditions due to pathologic changes in the subcutaneous fat. The most common of these has been known as scleroderma of the newborn, but in recent years is described under the more accurate name of traumatic subcutaneous fat necrosis. It is characterized by the occurrence of isolated areas of induration of the skin varying in size from as small as a dime to as large as the palm of your hand or even larger. It has a woody hardness with sharply defined margins and when palpated feels like a button that can be grasped at the edges with the fingers and moved back and forth. It is not attached firmly to the deeper tissues and the surrounding skin feels normal to the touch. The overlying skin seems firmly attached to the indurated mass and is smooth, it may have a normal color but more often has a

slightly reddened and sometimes a purplish hue. The infant usually shows no sign of discomfort when the lesion is palpated, but at times there does seem to be some tenderness. There are, as a rule, no constitutional symptoms.

The most frequent sites are the cheeks and the neck. These are the results of trauma from forceps blades. Other rather common sites are the back, especially the upper part between the shoulder blades, the upper arms, the front of the chest, and the thighs. These are all areas where trauma can and does occur in the handling of the infant at birth, just in the usual necessary manipulations and in such procedures as resuscitation.

The clinical course is a benign one with no symptoms and the lesions disappear spontaneously after a few weeks or at most two or three months. In some instances, however, the necrotic fat becomes liquefied and a fluctuant swelling results which may either subside spontaneously or rupture through the skin and discharge a light yellow fluid mixed with flecks of debris of decomposed fat. Healing takes place without incident but usually rather slowly.

There have been a few instances in which an infection of the affected tissue has occurred. The picture then is that of an extensive cellulitis, the skin is red and hot and the inflammation spreads rapidly over a wide area. There are marked constitutional symptoms with high fever and general prostration. Areas of fluctuation appear within a short time and when they are incised a large amount of purulent material is evacuated together with much fatty debris. The clinical course in these cases is a stormy one but by no means hopeless, especially now that we have such drugs as the sulfonamides and penicillin available. I have personally seen three such cases with involvement of extensive areas over the back in two, and over the back, lower abdomen and the thighs in the third. All three patients recovered and only the third one was lucky enough to get any specific treatment. This patient received both sulfadiazine and penicillin. The astonishing thing in these cases was that the process remained localized to the subcutaneous fat. The underlying fascia covering the muscles was not affected nor was the overlying skin except where incisions had been made or where spontaneous rupture with evacuation of pus had taken place. After the purulent and decomposed and liquefied fat had been evacuated there was a huge canopy of loose skin entirely unattached to the muscle and fascia which formed a roof over the abscess cavity. A probe could be freely moved in this cavity through an arc of 6 or 8 inches. The roof or canopy of loose skin remained healthy and subsequently became firmly attached and retained a normal appearance. We have never seen this phenomenon in any other age group and believe its occurrence is only possible because of characteristics of the physiology of the subcutaneous fat peculiar to the newborn.

MISCELLANEOUS CONDITIONS

Sclerema Neonatorum—Sclerema of the newborn is an entirely different condition from what we have just described although its occurrence is probably also due to peculiarities of the physiology and chemistry of the subcutaneous fat of the newborn

It occurs almost exclusively in premature or congenitally weak infants and is characterized by a woody hardness of the skin over the entire body. There is usually great general debility with very low body temperature. There is no known treatment and death occurs in a few days.

Scleredema Neonatorum—A condition in which there is also a quite marked hardness of the skin which however has a fairly good prognosis is known as generalized scleredema. In this disturbance the skin is definitely full and swollen and while it is very firm, pitting of the skin is possible. The body temperature is not subnormal and the infant does not appear especially sick. The condition is usually seen in premature infants but also at times in the full term. The prognosis is generally good but depends upon the general state of the infant in other respects.

Here again the etiology rests on physiologic and chemical conditions peculiar to the newborn, this time in regard to his water economy and acid-base equilibrium. It is characteristic of the newborn that he is hydrolabile, he retains fluids in his tissues easily, and he also may give them up easily.

Local Areas of Edema—Local areas of edema occur quite commonly in the newborn. The usual sites are over the pubic area, the dorsum of the feet and sometimes the dorsum of the hands as well, and the lower legs. A pitting edema over the mons veneris or the dorsum of the feet is in fact quite common in otherwise healthy full term infants. The condition may persist for days. It has no clinical significance and disappears spontaneously and no treatment is necessary.

Mongolian Spots—Quite frequently in white babies and almost universally in Negroes and in Mongolian babies we see Mongolian spots. These are areas of bluish gray or slate colored pigmentation of variable size most frequently found over the sacrogluteal area. They may, however, be scattered over other parts of the body, for example, over the deltoid area, on the ankles or on the wrists, over the dorsum of the hands or of the feet, sometimes the entire dorsum of the trunk is covered. I have never seen them on the ventral surface of the trunk except in the pectoral area a few times, nor have I seen them on the inner aspect of the thighs. These so-called Mongolian spots or "blue birth spots" are due to the presence of specific large pigment cells in the middle and deep layers of the corium. The spots tend to disappear in the course of two or three years, that is, they disappear from view because the overlying epidermal pigment gradually obscures them. Their occurrence is an atavistic phenomenon. When they ap-

pear in a Caucasian baby it is usually the result of an admixture of Mongolian blood somewhere back in the ancestry. It is, for example, quite commonly observed in eastern Europe (Hungary, Poland, Austria, Yugoslavia) while in western Europe it is seldom seen. It is quite commonly seen in the American Indians and in the Mexican Indians.

Congenital Skin Defects—Congenital skin defects occur much more frequently on the scalp than anywhere else but may occur on rare occasions on almost any part of the body. The characteristic examples are the dime to nickel sized, warty or smooth hairless spots on the vertex near or at the whorl of the hair. They are said to be due to amniotic adhesions and perhaps they are, but we have no positive proof for this belief. The defect is not always limited to the skin, it may affect deeper tissues.

Telangiectatic Nevus (Nevus Flammeus)—In conclusion I would like to discuss briefly the most common of all birthmarks, the so-called "stork bite." This is a superficial vascular nevus, found very commonly at the nape of the neck often extending slightly into the hairy scalp. Other favorite sites are the forehead, particularly over the glabella, the upper eyelids, the wings of the nose and the upper lip. They are significant only because they worry the parents since they tend to detract from the child's beauty when on the face. The parents can, however, be reassured in this regard since these nevi tend to fade out and usually disappear before the end of the first year.

RHEUMATIC FEVER, DIAGNOSTIC CRITERIA, AND RHEUMATIC HEART DISEASE

H WILLIAM FICHAMMER, M.D., I A.C.P.*

In presenting these patients I wish to bring out the nature of rheumatic fever in childhood, to consider the findings necessary for the establishment of a definite diagnosis and to discuss rheumatic heart disease.

CASE I

The first patient is a boy six years of age, who was brought to the Clinic ten days ago because of tiredness lack of appetite low grade fever recurrent nose-bleeds, and frequent pains in the arms, legs and abdomen. The mother stated that the boy had been in good health until six months ago. During the past winter he had had recurrent colds and severe tonsillitis with swelling of the lymph glands of the neck on two occasions.

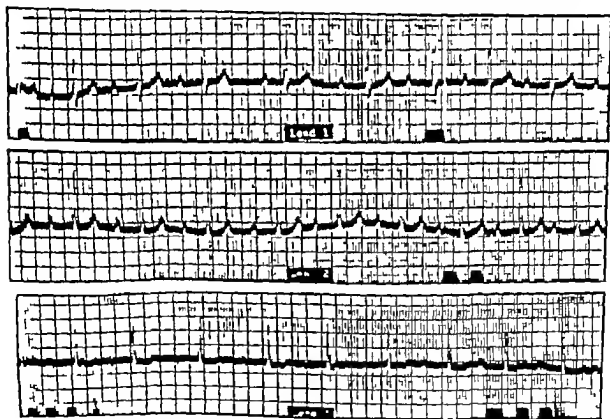


Fig 1—Electrocardiogram in Case I, showing prolonged P R interval, 0.32 sec onds and diphasic T wave in Lead III

Physical examination revealed a fretful blond blue-eyed boy not acutely ill. There was a distinctive pallor of his face. General nutrition was below par and the flesh was soft and flabby. The tonsils were hypertrophic and injected. A strands of lymphoid tissue were seen in the posterior pharynx. The pos-

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terior cervical chain of glands were numerous and enlarged. The anterior cervical glands were only moderately enlarged. Tenderness along the sternocleidomastoid muscle was present. The mucous membrane of the anterior nasal septum was congested and on the right side a bloody crust was present, giving evidence of recent hemorrhage. Heart action was regular but rapid, there was no enlargement and no murmurs were heard. This boy is the third child in a family of five children, an older sister had chorea three years ago. The father has rheumatic heart disease, the mother is well. An aunt on the mother's side died of "heart trouble." The patient was admitted five days ago to the hospital for further study and observation.

His temperature on entrance was 101° F (rectal). Subjective symptoms similar to those I have already mentioned were present, with the additional complaint of localized pain in the right knee, left ankle and precordial distress. Laboratory findings obtained in the last few days show red cells 4,200,000, white cells 12,600, hemoglobin 13 gm., 72 per cent polymorphonuclears, 26 per cent lymphocytes, 1 per cent eosinophils, 1 per cent monocytes. The urine was clear, specific gravity 1.022, there was no albumin or sugar present and the microscopic examination was negative. Erythrocyte sedimentation rate was 40 mm in one hour (Landau). Electrocardiogram (Fig 1) showed prolonged P-R interval, 0.32 seconds, and diphasic T wave in Lead III. The tuberculin skin test was negative. Agglutination tests for the typhoid group and undulant fever were negative.

Diagnostic Criteria—As you will notice, the right knee joint and left ankle are tender but not swollen nor red or hot to touch. The apex beat is in the fourth interspace midclavicular line. There is no cardiac enlargement. The rhythm is regular, the first heart tone at the apex is loud and rumbling but no murmurs are heard. The clinical diagnosis upon admittance to the hospital was focal infection and suspected rheumatic fever. The diagnosis today is active rheumatic fever, mild polyarthrits, and rheumatic carditis. Are we justified in making this diagnosis?

We notice in the history the presence of rheumatic infection in the father and the older sister, and that one aunt died of "heart trouble." Rheumatic fever has a marked *familial tendency* and it is held by some that this tendency is definitely a hereditary phenomenon following the mendelian law. This hereditary predisposition to the disease, although modified by other factors, such as geographical location, nutritional state, and changes in environment, may make it possible to predict the occurrence of rheumatic fever. The presence of rheumatic fever in the family certainly should put us on our guard and as we watch these children we should constantly be on the lookout for the early signs and characteristic manifestations of this disease.

Rheumatic fever is essentially a childhood disease, and it is in the child that the disease presents its greatest variety of symptoms and manifestations. The highest incidence of onset is found between the fifth and ninth year. Occasionally in the older child as well as in the adult the onset is sudden, preceded by an attack of tonsillitis or respiratory infection, followed by severe pain, swelling and tenderness in one or more joints, associated with high temperature and marked constitutional symptoms. In many of these cases, however, what is regarded

as the onset of the disease is in reality an exacerbation occurring in a previously infected rheumatic individual

The vast majority of cases of this disease have an insidious onset The typical sequence of events is well demonstrated in the history and findings of our patient, i.e. tiredness, loss of appetite, irritability, distinctive pallor of the face, vague mild aching pains in the limbs and joints, accompanied by low grade fever and increased pulse rate. These findings are all due to toxemia and may either singly or combined be present in any toxic state, and do not permit us to go any further than the diagnosis of focal infection, toxic state, and suspected rheumatic fever. The additional symptoms of epistaxis, tenderness in several joints, precordial distress, together with increased sedimentation rate, moderate leukocytosis, and myocardial involvement, as evidenced by the electrocardiogram, definitely establish the diagnosis of active rheumatic fever, mild polyarthritis, and rheumatic carditis

Many of the symptoms and findings may be produced, as previously pointed out, by other conditions. Childhood tuberculosis may be eliminated by tuberculin tests and x-ray studies of the chest, leukemias, severe anemia and mononucleosis differentiated by morphological blood studies, and other subacute and chronic infections ruled out by the employment of specific agglutination tests

The *vague fleeting pains* of rheumatic fever, so called "growing pains," usually occur after rest and on attempt at motion. They are relieved by heat and the administration of salicylates. However, one should keep in mind that similar pain may be associated with other infections or postural defects. It often becomes necessary to differentiate the abdominal pain from acute appendicitis. This is a rather difficult task at times. A careful history revealing some rheumatic manifestations, the occurrence of the pain over a long period of time, together with an increased sedimentation rate enables one to make a diagnosis of "rheumatic abdomen," and save the patient the risk of surgery

Polyarthritis is not a common manifestation of rheumatic fever in children. When it occurs the most common sites are the knees, ankles and wrists, and it is usually rather mild in comparison to that seen in adults. The differentiation from acute poliomyelitis may be difficult, particularly during epidemics of the latter disease. In its severe form one should rule out the presence of osteomyelitis, septic arthritis, leukemia, purpura rheumatica and undulant fever

Chorea is generally accepted as a definite manifestation of rheumatic fever. The onset of this disease is very insidious and mild types may often be overlooked. We should realize that even mild attacks of chorea may be associated with severe rheumatic heart disease

Subcutaneous nodules, most commonly found along tendons of the back of the hands, elbows, knees, spine and occipital region denote active rheumatic process. These nodules occur in groups and are usually not tender or painful

The major manifestations of rheumatic fever are polyarthritis, chorea, subcutaneous nodules and carditis. Among the minor manifestations we include fever, "growing pains," abdominal pains, epistaxis, erythema marginatum and increased sedimentation rate. *The presence of rheumatic fever in the family strongly suggests the possibility of this disease in the progeny. The presence of minor rheumatic manifestations in the child, together with one or more major manifestations, makes the diagnosis of rheumatic fever quite certain.* The disease in its inactive state may be recognized by the finding of valvular damage and associated cardiac murmurs or the presence of manifest chorea.

CASE II

Our second patient is a girl ten years of age, who was admitted to the La Rabida-Jackson Park Sanitarium five months ago. Her past history reveals the onset of rheumatic fever at the age of eight years, evidenced by minor manifestations and mild polyarthritis. After three months' rest in bed she apparently had recovered from her active rheumatic fever and was allowed to attend school. In the spring of 1944 she developed chorea of moderate severity necessitating bed rest for six weeks. During the summer she was apparently well, although rather nervous and failed to gain in weight. At the time of returning to school in the fall she was found to have a systolic murmur at the apex transmitted to the scapular region, increased second pulmonic sound, and slight cardiac enlargement. The work in school soon became too difficult, the child, appearing listless and tired, would often refuse to attend school and preferred to rest in bed. She was admitted to the Sanitarium in January 1945 because of weakness, poor appetite, loss of weight, rapid pulse, and afternoon temperature of 101° F (rectal) (Fig. 2).

Physical examination revealed a pale, tired girl. The flesh was soft, the skin moist and clammy. The throat appeared normal, cervical glands not enlarged, lungs resonant and clear throughout. The apex beat, diffuse and rapid, was located in the fifth interspace outside the midclavicular line and there was a slight cardiac enlargement to the right. A prolonged, high pitched, loud systolic murmur was heard at the apex, masking the first heart sound, and an increased second pulmonic sound. Orthodiagraphic tracing confirmed the cardiac enlargement, and showed a prominent left auricle. The electrocardiogram, blood findings, and urinalysis were essentially normal. Erythrocyte sedimentation rate was 32 mm in one hour (Landau).

The patient was given the usual sanitarium care, i.e., absolute bed rest, acetylsalicylic acid, grains 15, with phenobarbital, grain $\frac{1}{2}$ three times daily, and offered a standard high protein, high vitamin diet. After three weeks her appetite improved and she began to gain in weight. Color returned to her face, she became cheerful and happy. The sedimentation rate decreased and reached normal values in about six weeks after her admittance. The heart decreased in size as shown by repeated orthodiagraphic tracings. The apex beat became more limited in area, the systolic murmur at the apex less loud and shorter, the first heart sound more audible and distinct. Her progress up to six weeks ago was very good and encouraging. However, in the middle of April she developed a pharyngitis with a temperature of 102° F lasting three days, followed by loss of appetite. The sedimentation rate, which had remained normal since the latter part of February and throughout her acute illness, became elevated three weeks following the acute attack of pharyngitis, and has ranged between 24 and 40 mm until four days ago when it dropped sharply to a low point of 5 mm. The sleeping pulse rate, previously 10 to 15 beats below the waking rate, began at the onset of the increased

sedimentation rate to approximate the waking rate. In the last few days the sleeping pulse rate has exceeded the pulse rate present while the patient is awake

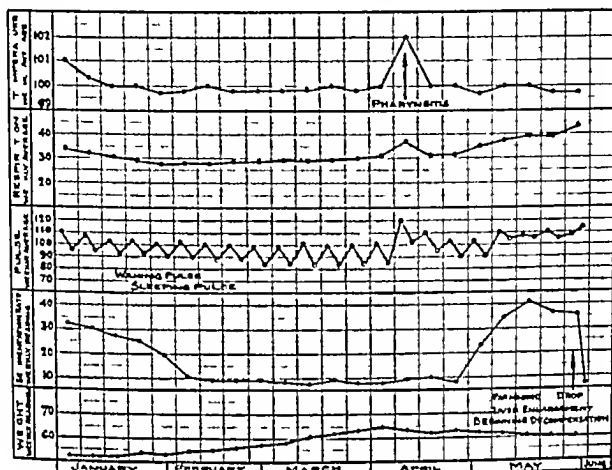


Fig 2—Clinical findings and course in Case II

Diagnostic Criteria—As you see this patient here this morning you will notice that she is pale and has a tired, worried look on her face. Her voice is weak and she seems short of breath. The main subjective symptoms are weakness, precordial distress and nausea. Her heart findings are the same as previously observed. However, we find at this time tenderness in the epigastrium and enlargement of the liver to two fingerbreadths below the costal margin. From these findings and the sudden marked drop in the sedimentation rate, we are able to diagnose beginning cardiac failure. May I again point out that we are unable to elicit any further findings in the heart or any sign of passive congestion in the lungs.

Considering this case in retrospect, it becomes evident that this patient's heart was involved from the very beginning of her rheumatic fever, that the insult to her heart is primarily that of myocardial damage, and only secondarily that of endocardial changes. The myocardial changes which are by far the more serious are directly associated with the length, severity and recurrences of the rheumatic process. It is evident that in the rheumatic child we are dealing with an active systemic infection. We are concerned with the effect of this infection upon the connective collagenous tissues throughout the body and especially within the myocardium. Valvular changes may take

place in due time, produced by proliferative and scarring lesions of the endocardium covering the leaflets, but they are only of secondary importance. The presence or absence of murmurs per se is of little diagnostic or prognostic significance.

The correct determination of the activity of the infection is of paramount importance in order to treat these patients adequately, to know when they may be given ambulatory activities and to evaluate their progress and their prognosis. Aside from clinical improvement, the subsidence of fever, the return of the blood picture to normal, and normal relation between waking pulse rate and sleeping pulse rate, we have found the erythrocyte sedimentation rate to be in most cases a reliable test for the determination of the activity of the rheumatic infection. In all cases of rheumatic fever the sedimentation test should be employed routinely, repeated at weekly or biweekly intervals. By this we may follow the progress of the disease, detect exacerbations early, even before clinical findings are evident, and as in this case determine beginning cardiac failure. It has been our experience that cardiac failure almost always occurs at the height of the infection, rarely if ever, as in adults, from myocardial strain imposed upon the heart from valvular lesions or general bodily exertion. The paradoxical drop in the sedimentation rate at the inception of cardiac failure has not as yet been satisfactorily explained. It is of interest that the enlargement of the liver occurs simultaneously with this drop in the sedimentation rate and prior to any other signs of increased venous pressure or cardiac changes. *Clinically the enlargement of the liver and the presence of tenderness in the epigastrium are of greatest importance and serve admirably as a guide in estimating the functional state of the heart.*

TREATMENT

The treatment and successful management of the rheumatic child depends on a thorough understanding of the nature of the disease on the part of the physician and continued education of the public. The recognition of the insidious onset of rheumatic fever and its variable clinical manifestations will insure early attention and diagnosis. A general understanding of the chronicity and tendency to recurrence of the disease will promote careful medical supervision and thorough periodical physical examinations over a long period of time which is most essential in order to achieve success in the fight against this common crippling disease of childhood.

Prophylactic Treatment—The various predisposing factors met with in the etiology of rheumatic fever suggest many measures to be considered in the prophylaxis of this infection. Adequate clothing, avoidance of chilling and exposure to dampness and cold are of great importance. A well-balanced daily routine in regard to play, work and rest, regularity of meals is very essential. Unfortunately children of pre-age are often allowed to dispense with the afternoon rest, many

are sent to the kindergarten in the afternoon and are occupied with additional work, such as music lessons and dancing. Recreation of a negative form, such as movies and radio programs, are allowed to occupy an excessive portion of the child's daily life.

Children with history of rheumatic fever in the family should be given particular attention. Common colds, pharyngeal infections, tonsillitis and childhood diseases, as we well know, often initiate rheumatic infection. Convalescence from these diseases should be prolonged beyond the time usually allowed and we should be on the alert for the appearance of early signs and manifestations of acute rheumatic fever.

The overactive nervous child, a rather common clinical entity, who does not respond to the ordinary management of rest and routine is often found to have a chronic infection of the upper respiratory tract. Such conditions as repeated colds, otitis media and tonsillitis, I think should be given particular attention.

The removal of chronically diseased tonsils and adenoids is not in itself a means of preventing rheumatic infection. I think that there are times when the removal of tonsils and adenoids may be harmful and even disastrous to the child. However, if the child presents no systemic infection, during the favorable season of the year—that is, early summer—definitely diseased tonsils and adenoids should be removed from standpoint of general health and of relieving the child of this burden.

We are accustomed to regard a normal gain in weight as being an indication of optimum health, therefore we should give particular attention to the child who is not making the usual increase in growth and weight. Being undernourished increases the hazards of the child in regard to acute rheumatic infection.

Since a cold and damp climate frequently plays a prominent role in the predisposing etiology, it may be advisable to remove certain types of children to a warmer climate in order to save them from acquiring this disease.

Treatment During the Active Stage—Treatment of rheumatic fever during the active stage consists mainly of bed rest, attention to nutrition and relief of symptoms. *Rest and relaxation* are necessary to reduce metabolic expenditure and to promote the development of the natural defense mechanism. Merely keeping the child in bed, often under duress, is not indicative of rest and relaxation. The child as well as the family should be informed of what we are trying to accomplish, the program well explained and accepted both by the patient and those who are to attend and care for the child.

A general *diet*, moderately low in carbohydrate, with the addition of vitamin D in the form of cod liver oil, will suffice. Of late a great number of vitamins have been suggested but I think we can truthfully say that a well balanced diet has proved quite satisfactory. A

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high carbohydrate diet tends to induce sudden increase in weight but not the type of growth that is indicative of resistance

Salicylates in some form or other are most commonly employed. They have a very definite beneficial effect on fever, muscle and joint pains and seem to have a direct action upon the exudative phase of the pathological process. However, we cannot ascribe any specific action to this drug. Moderate dosage, such as 10 to 20 grains three times daily, depending upon the severity of the disease and the age of the child, is to be preferred. *Salicylate* poisoning although rather rare should be watched for. *Chemotherapy* has given universally disappointing results and we may state that sulfonamides are distinctly contraindicated during the active stage of the disease.

The treatment of *chorea* has undergone many variations. Fowler's solution so popular years ago has been entirely discarded. *Nirvanol* with its toxic reactions likewise has been discontinued as well as fever therapy, due to the fact that the treatment in most instances is more severe to the patient than the disease itself. Bodily as well as mental rest with the use of sedatives, such as phenobarbital, bromides and chloral hydrate, has proved to give the best results. We have found warm baths or warm packs given twice daily to be very beneficial. The inducement of purposeful movements, such as attempts by the patient to feed himself, to handle objects and to walk around the bed, has shortened the period of incoordination and muscular weakness.

Treatment of Acute Rheumatic Heart Disease (Carditis)—The treatment of acute rheumatic carditis is essentially the same as that of the acute stage of rheumatic fever. As previously pointed out, heart failure in children differs from that in adults in that the infection is the principal cause rather than mechanical stress and strain. In other words, cardiac failure or decompensation always occurs at the height of the infection. Right sided failure with dyspnea is the common type. We rarely see generalized edema.

Absolute bed rest is imperative but we should allow the patient to assume whatever position he finds most comfortable. He should be handled cheerfully, allaying his fears with reassurance. *Salicylates* should be administered if tolerated, together with *sedatives*, even codeine and morphine, if deemed necessary. In cases without demonstrable edema the use of *diuretics*, such as *salyrgan*, 0.5 to 1 cc intravenously every three days, or *theocalcin*, 7½ grains twice or three times daily, often prove to be very effective. We have had very disappointing results with the use of *digitalis* and feel that in some instances the administration of this drug has shortened the patient's life. The intravenous injection of a 20 per cent glucose solution is an excellent supportive treatment.

Convalescent Care—When the patient is free of pain and has recovered from the acute stage of the disease, and begins his convalescence we are confronted with the most difficult part of the manage-

ment. Although the convalescent care may take months, we should assure the patient that the restrictions necessary are only temporary. With gradual increase in activities and provision for school work at home or in institutions, we are able to enlist the cooperation on the part of the child and to prevent the development of psychological problems. We have found the sanatorium care for convalescent rheumatic children to be of greatest value and in some cases indispensable. When the infection has become latent or inactive, as judged by clinical improvement and return of the sedimentation rate to normal, the child should be given graded activities, such as sitting up in a chair for a half hour twice daily, taking his meals at the table, bathroom privileges, one hour up and around in his room. During this increase in activity, the child should be carefully watched for any signs of rheumatic activity which if it occurs necessitates return to complete bed rest. Unnecessary prolonged bed rest imposed on account of the presence of cardiac murmurs or of "heart trouble" is to be criticized.

The *prevention of recurrences* of rheumatic infection is of the greatest importance. Our aim is to keep the rheumatic fever in an inactive state. By so doing we are able to save the child from any further damage, materially prolong its life and return the growing individual to normal life and activity.

Resistance to disease may be said to be an indicator of optimal health. To insure health we must carefully supervise the daily routine in regard to the quality and quantity of the diet, determine the safe "carrying load" of work, i.e. studies, bodily exercise and to provide adequate rest and sleep. Reactivation of the disease is usually associated with hemolytic streptococcal infections, therefore these children should be guarded against exposure to infections of this kind. Whenever the rheumatic child acquires an infection it should receive vigorous antistreptococcal treatment in the form of adequate chemotherapy. The sulfonamides should be continued until the streptococcal infection is definitely conquered and then followed by the administration of salicylates. These children should be carefully observed for four to five weeks following streptococcal infections. Continued salicylate medication may mask the presence of an exacerbation. It is, therefore, advisable to discontinue the medication for a period of time and then evaluate the clinical and laboratory findings before deciding if the child escaped an exacerbation and if the rheumatic fever is latent or in an inactive state.

The *prolonged prophylactic use of sulfonamides* has of late been advocated and used to a great extent. In patients with low resistance and marked susceptibility to repeated streptococcal infections, where control management and isolation has failed to bring about immunity response, the protective use of chemotherapy may be employed. However, we should keep constantly in mind that the use of sulfonamides does not improve the host, their action is directed entirely against

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the attacking streptococcal organisms. There is also danger that the streptococcal organisms may adjust themselves to the drug, i.e., become sulfonamide-fast. If this occurs and our patients become infected with such strains of streptococci, a very serious situation results.

SUMMARY

Rheumatic fever is essentially a childhood disease and it is in the child that the disease presents its greatest variety of symptoms and manifestations.

The rheumatic infection produces a chronic inflammatory process of the collagenous connective tissues throughout the body involving first and foremost the heart, often the joints, the subcutaneous tissue, the brain and other organs.

The disease has a marked familial tendency and the susceptibility seems to be definitely a hereditary phenomenon following the mendelian law.

The onset of rheumatic fever in children is usually insidious and during the active phase of the infection some cardiac involvement is always present. In over half of the cases such involvement is evidenced by clinical findings, in practically all cases it can be demonstrated by cardiographic and fluoroscopic studies.

The severity and persistency of the rheumatic infection determines the degree of cardiac damage and the course of the disease.

Erythrocyte sedimentation rate is a reliable test for the determination of activity of the infection. It should be routinely employed in all rheumatic patients, serving as a guide to treatment, management and prognosis.

The paradoxical drop in the sedimentation rate together with enlargement of the liver furnishes an early and reliable indication of beginning cardiac failure.

The treatment and successful management of the rheumatic child depends on a thorough understanding of the nature of the disease on the part of the physician and continued education of the public. The recognition of the insidious onset of rheumatic fever and its variable clinical manifestations will insure early attention and diagnosis.

Treatment during the active stage of the disease consists mainly of bed rest, attention to nutrition and relief of symptoms. Salicylates have a very beneficial effect on fever, muscle and joint pains and seem to have a direct action upon the exudative phase of the pathologic process. The treatment of acute rheumatic heart disease is essentially the same as that of the acute stage of rheumatic fever. Cardiac failure occurs at the height of the infection and differs from failure commonly seen in adults.

Convalescent care should be prolonged over a period of many months and is most successfully carried out in a sanatorium for rheumatic children.

THE CLINICAL SIGNIFICANCE OF HEART MURMURS IN CHILDREN

STANLEY GIBSON, M.D.*

It would seem appropriate to preface any discussion of heart murmurs with an apology. Perhaps there is no other phase of the physical examination of the patient in which the personal factor enters to the extent that it does in the practice of auscultation of the heart. It is doubtful whether any two individuals are endowed with the same ability to estimate the intensity, quality and pitch of heart murmurs. Even though two individuals may agree in general as to the character of an abnormal sound, they may yet disagree as to its significance. On the other hand, different examiners may not be in complete agreement as to the nature of the sounds heard and yet be in agreement as to the underlying pathology. There is no substitute for experience in the evaluation of heart murmurs, and this experience must include a large number of cases followed to the postmortem room.

In spite of the difficulties involved, heart murmurs are sufficiently important to merit special study. I have little patience with that school of cardiologists which teaches that murmurs are of little moment and that attention should be focused chiefly upon the amount of work which the heart is able to do. I have equally little patience with the physician who is so intent upon an abnormal sound in the heart that he neglects other means of examination. The electrocardiogram, the x-ray, the determination of function are all important, and it cannot be too strongly emphasized that auscultation is only one feature of the cardiac examination. I should like to add, however, that at least in children it is the most important single feature. Moreover, the evaluation of abnormal cardiac sounds in children requires a different approach from that which one uses in the adult. One wants to know first of all whether the child has heart disease. If he has heart disease it is important to know the cause, for the management of the child is to a great degree dependent upon the etiology of the cardiac ailment. It is my firm conviction that in answering these questions a careful evaluation of the murmur or murmurs heard yields more information than any other single method of examination. If any physician will recall his personal experience I think he will agree that in most instances where a question of heart disease in childhood has

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brought out conflicting opinions the discussion has usually revolved about the significance of a cardiac murmur

TECHNIC OF EXAMINATION

The technic of auscultation of the heart in infancy and childhood is important. It goes without saying that the examination will be unsatisfactory, or even worthless, if the patient is crying. Few of us have escaped the embarrassment of missing heart murmurs in young babies only to hear them so loudly at a subsequent examination that we can be morally certain that they did not develop during the interval. Occasionally in babies one must wait until they are asleep before a satisfactory examination can be made. The child who is nervous and apprehensive may show a murmur which will become less marked or completely disappear when the heart quiets down.

It should be an invariable rule to examine each patient in the supine position. He should also be examined in the left lateral and in the sitting positions. Inasmuch as the transmission of a murmur may give a clue as to its origin, it is important to listen in various directions from the point of maximum intensity, including the right side of the chest and the back.

FUNCTIONAL MURMURS

Heart murmurs are so frequent during the period of childhood that even in a well child the absence of a murmur rather than its presence occasions surprise. These murmurs are variously spoken of as accidental, functional or physiological, the inference being that they occur in the absence of organic involvement of the heart. These innocent murmurs have certain characteristics which usually enable one to distinguish them from organic murmurs.

The most frequent functional murmur is that which occurs in the second left interspace over the pulmonary area. This murmur is systolic in time, of short duration, of slight intensity, and is quite localized. It is not heard in the back. It is usually more clearly heard in the lying than in the sitting position. It varies with change of heart rate, and from one examination to another. It is distinguished particularly by its softness, its shortness and its localized character.

Another functional murmur slightly different from that described above is often heard medial to the apex at about the third left interspace. It is slightly harsh or somewhat "squeaky" in character but otherwise has the same qualities described above, namely, it is well localized, varies in intensity on change of position and of heart rate, and from one visit to another.

When the above murmurs are audible only on careful auscultation one can feel reasonably confident that they are without significance.

When they are fairly loud, differentiation from organic murmurs may be more difficult. Yet if one keeps in mind the location, the timing and the characteristics of these murmurs as mentioned above it is usually possible to arrive at a satisfactory decision. In some instances however, a murmur must be followed for years before it can be stated with reasonable certainty whether it is functional or organic.

It has been my opportunity, together with my colleagues in the cardiac clinic, to follow over a period of years a large number of children with murmurs such as I have described. It has been our experience that the great majority of these murmurs have become less distinct or have disappeared altogether at the approach of adolescence. Only rarely have they become more intense and taken on the quality of organic murmurs.

Closely related to the type of murmur described above is that which is encountered in children who are ill but in whom there is no evidence of cardiac involvement. I refer to the murmurs which are often spoken of as *benign*, namely, those occurring in the anemias, in the presence of fever, and various other conditions in which the heart may be temporarily affected by disease elsewhere. The fact that such murmurs become less distinct or disappear as the child's general condition improves is convincing evidence of their nature.

Sounds Sometimes Confused with Murmurs—A word should be said at this point concerning certain sounds which are unimportant except for the fact that they are sometimes confused with murmurs. The most important is the *venous hum*. It is a blowing or roaring sound, continuous throughout the cardiac cycle, best heard in the neck, and more intense on the right side of the neck than on the left. Confusion may arise from the fact that this hum may extend down over the chest, and if heard on the left side may be confused with the continuous murmur of patent ductus arteriosus. Yet the differential diagnosis is easy. The venous hum is loudest in the sitting position. It is much less loud or may even disappear when the patient is lying down. It also varies in intensity when the head is turned from side to side. Finally, pressure over the neck veins obstructing the flow of blood causes the hum to disappear. It is well to remember that such a sound does occur. More than once I have seen the diagnosis of patent ductus arteriosus made because of unfamiliarity with the characteristics of the venous hum.

There are other adventitious sounds which may occasionally occur in the cardiac area. One of these is a so-called "click" which may be heard at some point in the cardiac cycle. The origin may be obscure. In some instances at least the sound seems to be due to the sudden forcing of air from alveoli of the lung adjacent to the heart. There are also occasional whistling sounds heard over the precordium which may possibly be due to aberrant chordae tendineae.

MURMURS OF ORGANIC HEART DISEASE

In evaluating the murmurs due to organic heart disease it is essential first of all to be familiar with the pathological lesions which occur in the heart of a child. With few exceptions these lesions are due either to congenital or rheumatic heart disease.

Congenital Heart Disease—At the very basis of an understanding of congenital anomalies of the heart is an appreciation of the fact that in the great majority of instances there is an abnormal communication between the systemic and venous circulations. There are three common avenues of communication—a defect of the interventricular septum, an open foramen ovale, or a patent ductus arteriosus. Their importance in the pathology of congenital heart disease is attested by the statistics of Abbott who found in an analysis of 1000 cases that existing alone or in combination with other lesions there were 257 examples of defect of the interventricular septum, 290 of open foramen ovale, and 242 of patent ductus arteriosus. The passage of blood through any one of these openings may give rise to a murmur. In at least two of these conditions the murmur is so characteristic that the diagnosis can be made with confidence in most instances.

In a *localized defect of the interventricular septum* one hears a systolic murmur maximum in the third to fourth interspaces just to the left of the sternum. This murmur is harsh in character and is usually widely transmitted. In well marked cases a systolic thrill can be felt over the area of maximum intensity of the murmur. This murmur is usually heard as soon as the infant is born, and remains constant throughout childhood. In a series of twelve infants and children coming to autopsy at The Children's Memorial Hospital in whom a defect of the interventricular septum was found, the typical systolic murmur described above had been noted in eleven cases. In the remaining one the infant was moribund on admission to the hospital and the physical examination was not completed.

Perhaps the most remarkable murmur in the entire field of cardiology is that which occurs in typical cases of *patent ductus arteriosus*. This murmur is best heard in the first and second left interspaces. It is heard through practically the entire cardiac cycle, though louder in systole than in diastole. It is harsh and rumbling and has been variously described as humming top, machinery, mill wheel, tunnel, and rolling thunder in character. It is usually accompanied by a thrill. Although this murmur when occurring in typical form is diagnostic of patent ductus arteriosus it is worthy of emphasis that the characteristic murmur is of slow evolution. I have never heard a humming top murmur in a newborn infant. We have been fortunate in having had the opportunity to follow from birth a number of infants who subsequently proved to have the typical findings of a patent ductus. In the majority no murmur was described in the early months of life. In

others a systolic murmur was noted. And in practically all cases a systolic murmur was the only one described during the first year of life. At some time during the second year a diastolic phase of the murmur was usually recorded, and the typical continuous roaring murmur was ordinarily noted by the second or third year. A few months ago a baby 6 months of age was admitted to the hospital with symptoms and signs of congenital heart disease. There was marked cardiac enlargement, cyanosis on crying, and a harsh murmur chiefly in systole, but with a distinct diastolic phase heard in the first and second left interspaces. It was our opinion that a patent ductus arteriosus was present. The baby came to autopsy. The diagnosis of patent ductus was confirmed at autopsy, and there was in addition a fairly large open foramen ovale. This is the only instance in which I have heard a definite humming top murmur in a patient under 1 year of age. Increased interest has been aroused recently in the subject of patent ductus arteriosus because of the numerous instances of successful ligation following the development of this operation by Dr. Robert E. Gross of Boston. It should be emphasized, however, that the presence of the typical murmur does not in itself constitute an indication for operative interference. Other criteria must be fulfilled.

In cases of *open foramen ovale* there is less uniformity of opinion as to whether a murmur occurs, and if so whether it is sufficiently characteristic to be regarded as diagnostic. The contraction of the auricles is relatively feeble and the difference in blood pressure between the chambers is not great. One can easily imagine that a fairly large open foramen might exist without the transference of a sufficient amount of blood at a velocity which would produce a murmur. One sees at autopsy not infrequently a physiologically patent foramen ovale where no murmur had been noted during life. On the other hand, I have seen two instances in which a loud systolic murmur best heard in the second and third left interspaces was heard by numerous observers over a period of years and at autopsy the only abnormal finding was a large open foramen ovale. In these cases a defect of the interventricular septum had been suspected.

In summary, then, it may be said that of the three common lesions which allow of mixture of arterial and venous blood, the diagnosis of two, namely defect of the interventricular septum and patent ductus arteriosus, can be made with a good deal of assurance when they exist in pure form. Where more than one of these lesions exists in the same individual or where one of them occurs in combination with some other anomaly, the resulting murmur or murmurs produced by the passage of blood through two or more abnormal openings may leave doubt as to the exact origin. A classical example is the *tetralogy of Fallot*. In this condition there is both a defect of the interventricular septum and stenosis of the pulmonary artery. Under such conditions one cannot say to what extent each of these lesions contributes to the

precordial murmur which is heard in the tetralogy. The situation may be still further complicated by the fact that an open foramen ovale or a patent ductus may be present in addition to the other lesions. In such circumstances the diagnosis must be determined by other means such as the presence or absence of cyanosis, the x-ray silhouette, and the electrocardiogram.

In the absence of an abnormal communication between the systemic and venous circulations, murmurs due to congenital lesions may still occur.

Pulmonary stenosis may occur as a single lesion though it is relatively rare. In this condition one hears a systolic murmur maximum at the second left interspace, usually harsh in character, though the quality and transmission of the murmur will naturally depend upon the degree of stenosis. Congenital subaortic stenosis is a more frequent lesion, though by no means common. It is manifested by a harsh systolic murmur best heard in the first and second right interspaces and often accompanied by a thrill. Oftentimes a thrill may be palpated in the suprasternal notch when it cannot be felt over the aortic area.

At this point it may be well to mention the occurrence of murmurs in conditions of *heart strain* in which the essential pathologic changes lie outside the heart. One such condition is the adult type of *coarctation of the aorta*. The pathology consists of an abrupt narrowing of the aorta as if a string were tied tightly around it. The narrowing usually occurs beyond the origin of the great vessels of the arch at about the point of insertion of the ductus arteriosus. Theoretically one would anticipate a characteristic murmur at the base of the heart. In practice we have not found this to be true. It has been my privilege to observe some fifteen children with coarctation of the aorta. The striking feature has been the variability of the auscultatory findings in these children. A murmur has usually been present. Most often it has been systolic, sometimes in the second interspace, sometimes at the third left interspace, and other times at the apex. In one instance systolic and mid-diastolic murmurs were heard near the apex, closely simulating rheumatic heart disease. In one patient a diastolic murmur was heard along the left sternal margin beginning with the second sound such as is usually heard in aortic insufficiency. It was our suspicion that this may have been due to a bicuspid aortic valve which is known to be a frequent accompaniment of coarctation of the aorta. Of course one cannot make the diagnosis of coarctation of the aorta by auscultation of the heart. Yet the fact that one hears a murmur over the heart which does not fit into the usual pattern of either congenital or acquired heart disease should arouse one's suspicions. The diagnosis is made by the increased blood pressure in the arms, weakened or absent femoral pulsations, with lowered or unobtainable blood pressure in the legs, throbbing of the intercostal arteries and scalloping of the ribs on x-ray examination.

A second condition producing heart strain is that in which there is hypertension in the pulmonary circuit producing *dilatation of the pulmonary artery*. In this condition a diastolic murmur due to pulmonary regurgitation may occasionally be heard in the second left interspace although a murmur is not ordinarily present. In one patient who had decreased exercise tolerance, intermittent cyanosis and retarded growth a diastolic murmur was heard in the second left interspace. Autopsy revealed a huge pulmonary artery with relatively insufficient pulmonary valve, and the microscopic examination revealed primary proliferative arteriolar sclerosis of the pulmonary vessels.

Rheumatic Heart Disease—Let us now turn to a consideration of the murmurs which one encounters in rheumatic heart disease. Here again one must be familiar with the underlying pathology. Numerous post-mortem studies have established the fact that in rheumatic invasion of the heart the mitral valve is practically always involved. Hence it is necessary to direct one's attention to the murmurs which are produced by the inflammatory changes in the leaflets of this valve. Insufficiency of the mitral valve occurs early. It is manifested by a systolic murmur, usually soft and blowing in character, which is transmitted to the left. This murmur is oftentimes heard within a few days of the onset of the first symptoms of rheumatic fever. It is doubtful whether this early murmur is due to changes in the leaflets of the valve; it is probably due to relative insufficiency due to cardiac dilatation. The myocardium is regularly involved in the rheumatic assault upon the heart and is often of more serious moment than the valvular involvement. On this account early dilatation of the heart is to be expected. Whether the systolic murmur at the apex in the early course of rheumatic heart disease is due merely to stretching of the valve or whether it is due to an inflammatory process in the valve itself is after all largely a didactic question. The appearance of such a murmur in a heart previously known to be clear at the apex is presumptive evidence of rheumatic heart disease. If such a murmur persists for weeks or months after the acute rheumatic episode has subsided one can then feel fairly certain that the mitral valve has suffered permanent damage. This murmur is usually more distinct in the lying than in the sitting position and is oftentimes still better heard when the patient is turned on the left side.

Within a short time of the appearance of the systolic murmur, an early diastolic rumble may be heard. It occurs at a barely appreciable interval after the second sound, occupying in the cardiac cycle the position of the third heart sound. It is of short duration, is rumbling rather than blowing, and is usually quite localized at or near the apex. In the absence of marked cardiac dilatation this murmur is looked upon as reasonably definite evidence of mitral involvement. Months or years after the appearance of the first signs of mitral damage a third murmur may become evident. This is the familiar presystolic murmur

fection, and would naturally in the case of doubtful physical signs in the heart influence one in favor of a rheumatic cardiac involvement

Finally, the entire patient, not merely the heart, should be examined, and the use of x-ray, the electrocardiogram and other laboratory means should be employed as necessary to complete the diagnostic study

WHOOPING COUGH PREVENTION AND TREATMENT

LOUIS W SAUER, M D , P H D *

TRUE whooping cough is an acute infection of the respiratory tract caused by the whooping cough bacillus of Bordet and Gengou¹ (*Hemophilus pertussis*). Although it occurs most frequently during the first six years of life, it is fatal only during the first year or two. The cough is characterized by recurrent and persistent short expulsive paroxysms, which become progressively more frequent, prolonged and severe.†



Fig 3 —During a paroxysmal cough

The prodromal (catarrhal) period sets in with symptoms resembling those of the common cold. During the first weeks, often before quarantine is established, the disease is most highly contagious, because the germ is disseminated in greatest profusion early in the disease. Paroxysms usually occur more frequently during the night than during the day. For weeks attacks of expulsive hacks occur in close succes-

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† Lapin recently published a book, *Whooping Cough*.² Current monographs on whooping cough may be found in Brennemann's *Practice of Pediatrics* and in Litchfield and Dembo's *Therapeutics of Infancy and Childhood*

sion without time for the young patient to draw in breath, then, as air is drawn through the half-closed larynx the characteristic whoop is heard. In the period of decline, the paroxysms decrease in frequency and severity (Fig. 3).

DIAGNOSIS

To make an early diagnosis the clinician should be whooping cough conscious. A history of an intimate exposure to a known case of whooping cough, or the presence of an epidemic in the community, helps in making a diagnosis. In the absence of such leads, early diagnosis is difficult without resorting to the diagnostic laboratory. *Pertussis bacilli* aspirated by the nonimmune become lodged in the finer bronchi where they multiply rapidly during the week or more of the incubation period. A Petri dish or cough plate of Bordet-Gengou medium is held before the open mouth at the time of one or two expulsive coughs, then incubated for several days. The growth is then scrutinized for the minute colonies of the whooping cough bacillus.* When more than one child in a family is coughing, cultures should be taken only on the most recently ill.

The nasopharyngeal swab of Bradford and Slavin⁵ is a great convenience which facilitates the obtaining of cultures. The tightly plugged tubes (each containing a sterile swab) can be carried in the physician's bag and some can be kept available in his office. When a nonimmune patient with a suspicious cough is seen, the physician can take a culture without delay. The sterile, straight cotton-tipped flexible wire is gently inserted into a nostril until the tip touches the posterior pharyngeal wall. It is removed after one or two deep coughs, replaced into its sterile glass tube and sent to the diagnostic laboratory. Here it is swabbed over a Petri dish of Bordet-Gengou culture medium, and incubated at 37° C for about three days.

The minute, glistening, gray, elevated colonies of *H. pertussis* are best seen with a hand lens. Each colony is usually surrounded by a characteristic darker (hemolytic) zone (Fig. 4, A). Gram-stained smears examined under the oil immersion lens somewhat resemble influenza bacilli, but pleomorphism is absent and the presence of bipolar staining is decisive (Fig. 4, B, C).

Later in the course of the disease, white and differential blood counts are of diagnostic value only when the white cell count exceeds 15,000 per cm and the differential count shows a pronounced lymphocytosis. Absence of either does not exclude pertussis. If the cough persists and a whoop is not heard, a repetition of the blood counts after several

* Parapertussis, a less frequent disease, resembles mild whooping cough. It is caused by the closely related *Bacillus parapertussis* of Eldering and Kendrick.⁴ These two infections are differentiated solely by bacteriological and serological methods. Immunity to whooping cough, acquired by recovery from the disease or by the injection of Phase I *H. pertussis* vaccine, will not protect against parapertussis, nor will recovery from parapertussis protect against pertussis.

days might reveal the characteristic changes in the blood picture. Other tests⁶ such as complement fixation, agglutination and opsonocathopagic tests are of diagnostic value, but few laboratories are equipped to perform them.



Fig 4—*Hemophilus pertussis* A, Four zoned colonies ($\times 1$) B, Smear gram negative ($\times 1750$) C, Electron micrograph ($\times 50,000$) (Reproduced through the courtesy of Prof M H Soule Department of Hygiene, University of Michigan Ann Arbor)

PREVENTION

Delay in quarantine is an important factor in the spread of this disease to other nonimmunes of the community. An epidemic gets under way. Until recent years nothing was done to prevent whooping cough except to placard the house, confine the patient to the premises for three (or more) weeks after the onset of the characteristic cough, and prohibit visiting by nonimmunes.

Whooping cough can now be controlled as is diphtheria. It can be eliminated in any community (or institution) if the following three precautionary measures are carried out:

- 1 Early diagnosis and prompt quarantine of the patient
- 2 Isolation of intimately exposed nonimmune children (contacts) at least for the duration of the incubation period
- 3 Routine active immunization of all children soon after reaching six months of age, a stimulating dose of vaccine after known intimate exposure of the previously immunized child, also a prophylactic measure before starting school

Immunization Clinic.⁷—Since 1933, a municipally conducted whooping cough immunization clinic has been in operation in Evanston, a city of 70,000, adjacent to Chicago. Infants over six months of age are brought to the Infant Welfare Immunization Clinic at the Department of Health. Much of the credit for the elimination of pertussis is due to the cooperation of the nurses who contact the mothers and give them confidence in the project. On the first and third Wednesday afternoons of each month, from 1:00 to 3:00 o'clock, mothers bring their infants to the clinic. After signing a request slip, the mother takes her child to the physician seated in an adjoining room where he injects the first dose in the upper left arm after the site has been cleansed with 70 per cent ethyl alcohol on a sterile swab.

Sterilization of Syringes and Needles—Syringes and needles are previously sterilized by dry heat. A small, inexpensive (gas-heated or electric) oven with a thermometer in the door is satisfactory. Syringes and needles are previously cleansed in distilled water and dried, then placed into heavy-walled glass tubes with gauze in the bottom and firm gauze-covered cotton plugs (Fig 5). They are sterilized at 320° F

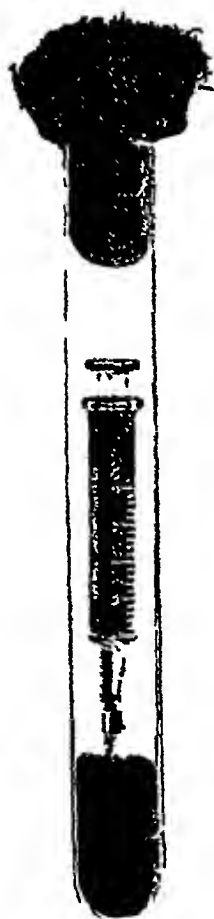


Fig 5—Syringe and needle in heavy-walled, well-plugged tube, sterilized by dry heat in an oven at 320° F for one hour, remain sterile for weeks and are immediately available

for one hour. Unless the plunger becomes contaminated (touching with the fingers), syringes may be reused throughout the afternoon. A separate sterile needle is used for each infant. Used needles are sterilized by boiling in distilled water for ten minutes before they are reused. If sterilization is carried out in a sterilizer or by boiling in distilled water for ten minutes in a covered enamel dish, the plunger and barrel should be separated. To prevent deleterious action on per-

tussis antigen, all water should be expelled from the syringe and it should be cool before any vaccine is drawn into it

An increasing number of local physicians have injected their infant patients with one or another commercially available pertussis vaccine. In recent years, the State of Illinois has made Phase I H pertussis vaccine available for free distribution. In the 1936 Annual Report of the Evanston Department of Health, Dr J W Pollard, then Commissioner of Health, said "For the last decade, the average yearly total of whooping cough patients reported was 334. In 1936, there were 91 cases, 90 had never been vaccinated against whooping cough. One case developed whooping cough through previous exposure during the period of inoculation. All children treated are referred by local social agencies, who vouch for the financial status of the families." The number of children injected annually has nearly approximated the number of new births. The only cases encountered in recent years were those in nonimmunized individuals who contracted pertussis elsewhere. The most frequent cases are older nonimmunized children who have moved into the community. Between 1938 and 1945, no child injected in Evanston is known to have developed whooping cough. During 1944, the only three cases reported had contracted the disease elsewhere, none of them had been injected prophylactically. Whooping cough has progressively decreased in Evanston and in 1944 practically ceased to occur.

Pertussis Vaccination in Early Infancy—Whooping cough is most dreaded when it occurs in infants. All data showed that especially among the infants of the city poor, is pertussis mortality high. Years ago Hoyne⁸ reiterated that for pertussis immunization to be most effective it should be started earlier than the sixth month of life. In an attempt to immunize younger infants several thousand less than six months of age were injected at The Cradle and at Chicago Department of Health Welfare Stations with vaccine. It was found that Phase I pertussis vaccine injected before the sixth month of life failed to protect against the disease. Most of these infants did not yet possess the power to develop adequate immunity when they were injected so early in life. Furthermore, some could not be injected during the first several months because they were "feeding problems," especially those born prematurely.

Sako, Treuting, Witt and Nichamin⁹ reported on injection of younger infants with an alum-precipitated pertussis vaccine. Their study included 3793 young New Orleans infants injected with three doses (0.2, 0.3, 0.5 cc.) at monthly intervals starting during the first month of life. The vaccine contained 40,000 million alum-precipitated bacilli per cubic centimeter. Their study totaled a twenty-six month period. During that time 19 per cent of the 141 exposed Negro children and 16.7 per cent of the eighteen exposed white children had developed pertussis. No deaths occurred in the vaccinated group as

compared to thirteen deaths among the nonvaccinated controls. They recommended that infants should be injected against whooping cough during the first months of life.

In recent years we, too, attempted to immunize young (Cradle) infants with three doses of an alum-precipitated pertussis vaccine. The pertussis complement fixation test was 3 or 4 plus positive in 31 per cent of 115 young infants several weeks after the final dose. Because nothing is known about the duration of immunity conferred so early in life, infants injected so early (before the sixth month) should be reimmunized soon after the seventh month.

Commercial H Pertussis Vaccines—The present status of pertussis vaccine as an immunizing agent is best reviewed by Felton and Willard¹⁰ in an authoritative Report of the Council on Pharmacy and Chemistry of the American Medical Association. Phase I H pertussis, may be plain or alum precipitated, or the vaccine may be mixed with plain or alum-precipitated diphtheria toxoid or with alum-precipitated diphtheria and tetanus toxoids. The number of commercial pertussis vaccines and mixtures of pertussis vaccine in plain and in alum-precipitated diphtheria toxoid and mixtures of pertussis vaccine in alum-precipitated diphtheria and tetanus toxoids has increased rapidly in recent years. * Pertussis vaccine of the proper concentration and dosage should confer prolonged active immunity if it has been properly prepared from Phase I bacilli, is kept refrigerated, and is injected after the sixth month of life. It has been firmly established that for infants less than six months of age only alum-precipitated pertussis vaccine should be used.

All investigators who have reported on a comparison of results with plain and alum-precipitated pertussis vaccine found a higher degree of protection with smaller doses of the latter. Substituting alum for at least half of the slowly growing pertussis bacilli appreciably lessens the cost and thereby makes possible a wider range of immunization.

Pertussis Vaccine in Diphtheria Toxoid—Bordet¹¹ was the first to inject a mixture of pertussis vaccine and diphtheria toxoid. Felton and Willard¹⁰ state "The combination of pertussis vaccine with diphtheria toxoid would be a convenient means of reducing the number of routine immunization injections generally recommended for infants and children." Since 1938, H pertussis vaccine in alum-precipitated diphtheria toxoid ("Diph-Pertussis" alum-precipitated) has been our

* Northwestern University Medical School has granted to Parke, Davis & Company the sole rights to prepare the following pertussis antigens according to the writer's detailed specifications: Authorized H Pertussis Vaccine Immunizing (15,000 million bacilli per cc—1, 2 and 3 cc doses), Authorized Pertussis Vaccine, Alum Precipitated (30,000 million bacilli per cc—0.5, 0.5 and 0.5 cc doses), and Diph-Pertussis Alum Precipitated (30,000 million bacilli per cc in double-strength toxoid—0.5, 0.5 and 0.5 cc doses) (Authorized "Triple" Antigens—H Pertussis Vaccine in Alum Precipitated Diphtheria and Tetanus Toxoids—30,000 million bacilli per cc in double-strength toxoids—will be available in 1946)

antigen of choice at the Clinic, at several orphanages and in private practice Schick tests and pertussis complement fixation tests six weeks or more after the final dose show that a very high degree of immunity is conferred. To date, no child injected with this product is known to have developed either disease.

Pertussis Vaccine in Diphtheria and Tetanus Toxoids—Several favorable reports¹² have recently appeared on "triple" immunization (against whooping cough, diphtheria and tetanus). Phase I H pertussis vaccine is mixed commercially with alum-precipitated diphtheria and tetanus toxoids. Three doses are injected at monthly or bimonthly intervals. The collected data seem to show that whooping cough vaccine and diphtheria and tetanus toxoids can be injected at the same time with satisfactory protection against each of these three diseases. The best results were obtained with the alum-precipitated mixture. The highest immunity response resulted when a time interval of one or two months was observed between the three doses. Diphtheria immunization is not effective during the first six months of life. "Triple" immunization should, therefore, not be begun before the child is old enough to develop specific antibodies against all three of the diseases, i. e., the infants should be at least seven months old.

Reactions—A systemic reaction is more likely to occur after the injection of plain than after alum-precipitated pertussis vaccine, because the entire dose is rapidly absorbed. It is, in the main, a transient fever, the peak occurring within twenty-four hours. The parent should be instructed that it might occur, that the child's temperature should not be taken, nor should local wet dressings be applied. A dose or two of aspirin and liberal amounts of water may be advised, if the child becomes restless.

Prevention of Alum Abscess—Until recent years, a local reaction was much more likely to follow the injection of alum-precipitated vaccine than after plain vaccine. Many health departments and physicians had hesitated to use alum-precipitated antigens because of the occasional occurrence of a sterile abscess at the site of injection. A residual nodule may be palpated, in some instances for weeks, but alum abscess has been almost completely eliminated by the following injection technic. The vial is shaken vigorously, the rubber cap is wiped with sterile gauze or cotton saturated with 70 per cent alcohol. After 0.5 cc. of air has been injected, the vial is inverted and gently shaken until the desired volume of vaccine is aspirated into the syringe. The site on the upper arm, lateral and distal to the deltoid muscle, is wiped with cotton or gauze saturated with alcohol. Since Sako⁹ and co-workers believe a dry needle point important in the prevention of alum abscess, any visible alum-precipitated antigen at the needle tip should be removed by wiping on sterile gauze. The needle, pointed distally, pierces through the skin parallel with the humerus (Fig. 6). The plunger is pressed slowly as the dose is injected deeply subcutaneous. The needle

remains in place for a few seconds before it is quickly withdrawn. Immediately a piece of sterile gauze (2 by 2 inches) is placed over the injection site. With the right index and middle fingers, from the point where the needle entered the skin, gently yet firmly stroke distally several times.

Stimulating Dose—Wu and Chu¹⁸ were the first to recommend that an immunized child intimately exposed to pertussis years later should



Fig 6—The infant offers the least resistance when held in the mother's firm embrace (heads turned away). To prevent alum abscess the needle is pointed distally. The tip should be free from antigen as the dose is injected beyond and lateral to the deltoid insertion. The arm remains in the injector's firm grasp until after the final distally directed massage stroke.

be promptly injected with a single stimulating (prophylactic) dose of pertussis vaccine.* This should stimulate specific antibody development and prevent the disease. This is now applicable also to subsequently exposed children immunized in infancy with mixed pertussis vaccine and diphtheria toxoid or with mixed pertussis vaccine and diphtheria and tetanus toxoids. For example, the school child immunized simultaneously against pertussis and diphtheria during infancy,

* Preferably 2 cc. of H pertussis vaccine (15,000 million bacilli per cc.)

when intimately exposed to whooping cough would be injected promptly with one stimulating (prophylactic) dose of pertussis vaccine. Likewise, the child, immunized singly or simultaneously against pertussis, diphtheria and tetanus in infancy, who years later gets a wound in the foot by stepping on a rusty nail would most likely be given very promptly a stimulating dose of plain tetanus toxoid, not the heretofore customary prophylactic dose of tetanus antitoxin which is made from animals. In this way the body should be stimulated to promptly develop sufficient tetanus antibodies to prevent the disease. Furthermore, the child would not have become sensitized to the alien (animal) protein. Anaphylactic reactions would thus be eliminated.

It has recently become customary, especially in larger cities, to routinely inject children immunized against whooping cough and diphtheria during infancy, with one stimulating (prophylactic) dose of the mixed diphtheria and pertussis antigen before they enter kindergarten or school. Children immunized during infancy against these three diseases, either singly or with "triple" antigens, should be injected with one stimulating (prophylactic) dose of "triple" antigens (pertussis vaccine in alum-precipitated diphtheria and tetanus toxoids) as a prophylactic measure.

Pertussis Skin Test—Of the various intracutaneous pertussis tests proposed from time to time only the Flösdorf¹⁴ agglutinin test has been found reliable in differentiating nonimmune and immune, especially after immunization with pertussis vaccine. The test is read one-half hour or twenty-four hours later. A positive test consists of induration or edema at least 10 mm. in diameter. It occurs only in the immune. The best time to perform the test is several months after the final dose of vaccine.

Passive Immunization—Because whooping cough is most likely to be serious in infants, and since active immunization with vaccine would be too time consuming, it is customary to promptly inject intimately exposed nonimmunized infants with human pertussis immune serum. The United States National Institute of Health at Washington has authorized its preparation and distribution. The Michigan State Department of Health has been preparing it for years for Michigan physicians. The Philadelphia Serum Exchange (1740 Bainbridge Street) a nonprofit human serum center at the Children's Hospital of the University of Pennsylvania, prepares and distributes vacuum-dried human pertussis immune serum. It is available to physicians everywhere. Physicians in the Midwest can obtain it through the Deutsch Serum Center, Chicago. When exposure is casual or of short duration 20 cc. are injected intramuscularly into the buttocks. When exposure is prolonged (i.e., over twenty-four hours), two 20 cc. doses should be given at three to five day intervals. This dose applies to all ages. The best results are obtained when the serum is injected early in the

incubation period Pertussis immune serum is prepared by pooling the blood of a number of healthy adults who have had whooping cough in childhood and whose protective substances have been "fortified" by repeated courses of Phase I Pertussis Vaccine For intramuscular use 20 cc of dried serum is dissolved in 10 cc of the diluent Complete protection results in a very high percentage of intimately exposed infants The passive immunity so conferred is only temporary Unless the infant develops the disease, further exposure should be avoided In addition to the serum, in order to develop the infant's own pertussis antibodies as quickly as possible, the three customary doses of Phase I Pertussis Vaccine should be injected subcutaneously in alternate upper arms within a week

Various commercially prepared pertussis rabbit serums and antitoxins have been proposed from time to time ¹⁵ Years ago Bordet cautioned against the use of animal pertussis antitoxins and serums Felton,¹⁶ in an extensive survey on pertussis serums for the Council on Pharmacy and Chemistry, says, "In whooping cough as in other infectious diseases there is advantage in using human serum rather than animal serum, in order to avoid sensitivity" Lapin¹⁷ recently warned of the potential dangers in animal-protein-containing serums and so-called pertussis antitoxins

TREATMENT

Although most pertussis patients beyond the age of three may not require much medical attention, infants and frail young children may contract more or less serious complications involving the lungs, the gastrointestinal tract or the central nervous system As soon as the diagnosis of whooping cough has been made with certainty the young patient should be isolated, preferably in bed, for at least five weeks In this way, secondary infections such as the common cold, measles and pneumonia are less likely to occur If the weather permits, fresh air and sunshine are desirable and the patient should be kept out of doors twelve or more hours daily Coughing and vomiting are usually made more severe by the breathing of cold air, by chilling, smoke, dust, overexertion, and by swallowing iced drinks or cold foods The food should be easily digestible, rich in vitamins, and proper for the age and digestive capacity of the patient Excessive fluids should be avoided When vomiting is persistent, small portions of farina or other cereals cooked in milk to form a thick paste are rather well tolerated Oral medication should then be decreased or entirely omitted Retention enemas of an ounce or more of tepid water repeated four or more times daily may be necessary, especially during high fever and persistent vomiting

Drugs—The age and weight of the patient as well as the severity of the disease or its complications should determine the kind of drug and dosage used It is not prudent to attempt to subdue completely parox-

ysms of coughing by medication Especially is this true in the infant and frail child Secretions should be coughed up and out of the bronchi at least several times daily Opium in any form should not be given to infants Phenobarbital ($\frac{1}{4}$ to $\frac{3}{4}$ grain according to age) may be tried every six to twelve hours for a week or more Prolonged sedation of infants and young children may induce bronchopneumonia To induce sleep and lessen vomiting, a child of four may get some relief from a teaspoonful of the following prescription given before retiring and repeated if necessary once or twice during the night. It may produce a flush of the body

Codeinae sulfatis	gr iv (0.24)
Saccharini	gr $\frac{1}{2}$ (0.03)
Tr belladonnae	gtt. xl (2.5)
Elix. phenobarbitalis	ad oz iv (120)

M et Sig—(keep bottle out of children's reach)

$\frac{1}{2}$ to 1 teaspoonful once or twice at night for severe cough

When vomiting is recurrent and the paroxysms severe, sleep and relief are often induced by a retention enema of sulfuric ether (25 per cent) in olive oil (75 per cent) given with a No. 14 F catheter and small bulb syringe every eight hours for a week or longer The usual dose is two teaspoonfuls of the mixture for each year of age It is inflammable. There is no danger of necrosis

Pertussis Immune Serum (Human)—McGuinness, Armstrong and Felton¹⁸ published an extensive report on the use of human pertussis immune serum in the treatment of pertussis in infants and frail young children. In severe cases several doses should be injected either intravenously or intramuscularly Vacuum-dried serum facilitates administration and insures against a decrease in antibody content as the result of storage. They recommend early injection of 20-cc. doses at forty-eight hour intervals regardless of age In seriously ill infants a fourth dose of 20 cc. is recommended about a week after the third dose to prevent a relapse. In critically ill infants, especially with bronchopneumonia, they give 60 to 100 cc. of serum intravenously at a dose, and repeat this large dose one or more times. The early use of liberal doses has greatly improved prognosis and effected a marked reduction in pertussis mortality The advantages of human over animal serum were enumerated under prevention after exposure. Use of human serum avoids sensitivity, especially in allergic individuals. This is important in infants ill with pertussis.

Treatment of Complications.—Periodic examinations of acutely ill young pertussis patients will reveal complications as they arise. Hospitalization is not recommended unless the patient has a complication which can best be treated there. The pertussis patient is generally not admitted to contagious disease hospitals not only because the patients are endangered but because the pertussis patient might contract a

cross infection which would postpone or impede recovery. The cubicle, an individual aseptic nursing technic, and bactericidal lamps, valuable wherever infants are housed, are essential in the prevention of respiratory complications in the young pertussis patient.

The most frequent serious complication involves the respiratory tract, especially in infants and frail young children. Besides repeated doses of human serum, sulfadiazine and penicillin are of value, if used early. The oxygen mask or tent should be used if cyanosis persists.

Sulfadiazine is the sulfa drug of choice because it is most effective and least toxic. For the greatest benefit it should be given sufficiently early. Although it is less likely to produce nausea, vomiting, drug fever and drug rash, it is not without toxic potentialities. Since it is slowly eliminated, excessive doses should be avoided. The oral route is preferred. The initial dose is $\frac{1}{4}$ to $\frac{1}{2}$ grain per pound of body weight (0.033 to 0.066 gm per kilogram). The maintenance dose is 1 grain per pound of body weight (0.13 gm per kilogram) for twenty-four hours. The drug should be continued in divided doses every six hours until the temperature, pulse rate and respirations remain normal for forty-eight hours. The dose is then halved for a day or two before it is omitted. A drug blood level of 10 mg per cent is usually adequate if maintained for at least several days. Plain water and sodium bicarbonate should be used in liberal amounts.

Sulfadiazine sodium should be administered intravenously only when the patient is severely ill or persistently vomiting, and an adequate blood concentration is urgent. The dose is based on $\frac{3}{4}$ grain per pound (0.1 gm per kilogram) in twenty-four hours. A 5 per cent solution is used. Five grams of the drug are added to 100 cc of sterile distilled water or isotonic saline. Other solvents such as glucose or plasma should not be used or added. The solution should not be boiled or autoclaved. It is customary to use ampules of concentrated solution which must be diluted with a definite volume of sterile distilled water or sterile saline just before it is injected intravenously. An initial dose of 0.25 to 0.75 cc per pound of body weight is advisable, and a maintenance dose of 0.5 to 1 cc per pound in twenty-four hours should be divided into two or three doses. This should be replaced as soon as possible by oral sulfadiazine 1 grain per pound of body weight in twenty-four hours (0.13 gm per kilogram) divided into doses at four to six hour intervals.

Penicillin is used in sulfadiazine-resistant or sulfadiazine-allergic pertussis bronchopneumonia patients when it has been found that the pulmonary complication is caused by some type of pneumococcus or streptococcus. Regardless of the dose or parenteral route of administration, a solution of penicillin should be made fresh daily and kept refrigerated at a temperature not over 50° F (10° C). The commonly recommended dilution is 100,000 Oxford units of penicillin in 20 cc of sterile normal salt solution (prepared with pyrogen-free distilled

water) Each cubic centimeter of this stock solution contains 5000 units and is suitable for intramuscular or intravenous injection. In infants and young children the intramuscular route is preferred. The customary dose is 2 cc injected eight times each twenty-four hours. To minimize local trauma, injections are rotated between the large muscles, such as gluteal, deltoid and thigh. Treatment should be continued for five to seven days. Fluids should be forced by mouth. A concentration of 5 mg per cent of free drug in the blood serum is usually adequate. The Rammelkamp¹⁰ technic may be used to determine the blood level. If improvement does not follow chemotherapy and human pertussis immune serum, pneumonia due to specific types of pneumococci should be treated also with type-specific antipneumococcic rabbit serum.

Gyorgy and co-workers²⁰ used penicillin by mouth buffered with sodium citrate. Their tablets contain 10,000 units of penicillin and 1 gm of trisodium citrate and are not practical for infants and young children. Burke and co-workers²¹ used aluminum hydroxide (Creamalin liquid) as a buffer. Two hundred thousand units of penicillin are dissolved in 40 cc of cold water, 60 cc of Creamalin liquid are added drop by drop with vigorous stirring. If kept refrigerated it is stable for at least twenty-four hours. The bottle should be well shaken before each dose is removed. The total oral dose is usually 150,000 units, one tablespoonful of the mixture (approximately 30,000 units) is given hourly for six doses. Complete fasting should be maintained during the treatment and for two hours after the final dose. If the administration of water is indicated (high fever), retention enemas are preferable but the amount should be limited.

The most effective treatment for convulsions is a hypodermic injection of sodium luminal or phenobarbital sodium ($\frac{1}{2}$ to 1 ampule according to age). If convulsions continue, spinal drainage should be resorted to.

Gastrointestinal complications such as enteritis require careful selection of the proper food. In young infants, during the acute stage, especially if the stools contain mucus and blood, only sterilized breast milk or protein milk should be prescribed. Sulfasuxidine in divided doses may be tried for several days.

SUMMARY

Whooping cough can be reduced and practically eliminated in any community if three cardinal factors are observed:

- 1 Earlier diagnosis (use of nasopharyngeal swab culture, cough plate, and white and differential blood counts)
- 2 More rigid isolation of exposed nonimmune infants and young children.
- 3 Immunization of all infants soon after reaching six months of age.

Commercially available pertussis antigens may be grouped as follows

- 1 Phase I H pertussis vaccine (3 doses, 1 to 4 weeks apart)
- 2 Alum-precipitated Phase I H pertussis vaccine (3 doses, 1 or 2 months apart, especially for very young infants)
- 3 Alum-precipitated Phase I H pertussis vaccine in diphtheria toxoid (3 doses, 1 or 2 months apart), has gained in favor rapidly in recent years
- 4 Alum-precipitated Phase I H pertussis vaccine in diphtheria and tetanus toxoids (3 doses, 1 or 2 months apart), the most recent trend seems to be toward the use of "triple" antigens

Human pertussis immune serum is safe and effective

- 1 As a prophylactic measure for intimately exposed nonimmune infants before symptoms occur
- 2 As a therapeutic measure in larger doses for infant and frail young pertussis patients

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IMMUNE SERUM IN THE PROPHYLAXIS AND TREATMENT OF VIRUS DISEASES

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INTRODUCTION

PERIODIC critical examination of even well established concepts contributes to medical progress. Such re-evaluation is particularly justified in those fields under intensive study. Virus diseases have attracted increasing scientific attention, and many contributions have appeared in recent years which help materially to a better understanding of the nature of virus diseases. Since the physician is concerned with prevention and treatment of disease, it may be opportune to review specific serum prophylaxis and treatment of virus diseases in the light of our present knowledge and experience ‡.

Viruses (and rickettsia) differ fundamentally from bacteria in that they are intracellular parasites. This property has long been thought to make the infectious agent immune to therapeutic measures. In practically all other respects, however, virus infections and immunity to virus infections are comparable to bacterial infections and immunity. As Rivers¹ says, "There is nothing peculiar about immunity in virus diseases. Principles that hold in other fields operate also in the virus domain." A brief reconstruction of the probable behavior of the virus in the susceptible host may throw more light on what may be expected from specific treatment.

The infectious agent enters the body through one or more portals of entry, usually the nasopharynx, intestinal tract or skin, and invades the body cells. Multiplication of virus in these body cells takes place. The virus, after a period of time, escapes from these cells and is transmitted through one or more pathways to other cells of the body.

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‡Joseph Stokes, Jr., proposes with good reason, that the term "treatment" be applied to the use of immune bodies after exposure to infection, and "prophylaxis" only before exposure takes place. In this paper, however, the terms will be employed in the orthodox manner, that is, "prophylaxis" applies to treatment during the incubation period before the acute disease, and "therapy" is used after the active disease develops.

The virus may invade adjacent cells, it may invade the blood and lymph stream, or it may extend along nerve fibers or by other means. The method of spread probably varies considerably in different infections and may play an important part in determining the efficacy of any specific therapy. Such continued spread and multiplication must be progressive until the infection reaches the maximum extent of cellular invasion. The infectious agent also leaves the cells and, in most diseases, is eliminated from the body through one or more portals of exit, such as the upper respiratory tract, the gastrointestinal tract, or the skin.

There are certain salient facts which must be reviewed briefly in order that specific prophylaxis or treatment can be judiciously considered.

1. Virus infections are followed by a variable amount of antiviral substance in the blood stream. Therefore, convalescent serums may vary considerably in potency.

2. For a serum to be effective, it must be rich in viral antibodies.

3. Immune serum can neutralize extracellular virus in transit and at the site of parasitized cells in the body.

4. Immune serum surrounding susceptible cells will probably prevent infection of these cells by virus.

5. In some diseases, if the virus has invaded cells, the presence of immune serum subsequently will not prevent the growth and multiplication of the virus in the cell.

Therefore, the cardinal principles that should govern efforts to treat virus infections are (1) the use of serum rich in immune bodies, (2) treatment instituted early in the illness before there is extensive cell invasion by virus, and (3) large repeated doses administered by a route which will bring the immune bodies rapidly in contact with the tissue cells.

Clinical and experimental investigation on the use of serum for virus infections is remarkably limited and the results have generally been considered disappointing. This is principally due to the general difficulties attending virus research, such as inability to grow the virus easily and abundantly so that hyperimmune serums could be produced, the low titer of viral antibodies in the serum following a natural infection, limited supplies of natural immune serum, and difficulty of early diagnosis of the natural disease.

Despite these handicaps, and despite the general concept that antiviral immune serums are valueless, studies have been pursued which bear out the value of specific serum therapy when full consideration is given to the behavior of virus infections and the nature of virus immunity.

MEASLES

Prophylaxis—The literature on the value of measles serum in prophylaxis is very large. First reported by Weisbecker² in 1894, the value

of convalescent serum is now well established. There is reason to believe that the measles convalescent serum must be rich in antibodies, because small doses are effective. This is confirmed in a recent publication by G. A. Orlov² who reports success in titrating immune serum by complement-fixation test against virus antigen obtained by oral washings from patients and emulsions of infected mouse lungs. Furthermore, this titration bears out the clinical experience that measles convalescent serum is much more potent than normal adult serum, for the author found convalescent serum to be approximately twenty times more active than serum from adults.

Measles serum prophylaxis demonstrates very nicely the time relationship of serum administration and the effect on the disease, or the

TABLE 1—MEASLES CONVALESCENT SERUM PROPHYLAXIS, SHOWING RESULT IN RELATION TO TIME OF ADMINISTRATION

Days Exposed before Serum Administration	Number of Cases	Outcome					
		No Measles		Modified Measles		Typical Measles	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
1	166	130	78	31	19	5	3
2	268	197	73	58	22	13	5
3	345	235	68	97	28	13	4
4	427	246	58	169	39	12	3
5	408	213	52	161	39 5	34	8 5
6	230	105	46	117	51	8	3
7	151	65	43	79	52	7	5
8	51	16	31	28	55	7	14
9	50	7	14	18	36	25	50
and over							
Total	2 096	1 214	58	758	36	124	6

serum inhibiting effect on the virus in the host. If the amount of serum is held constant, it will usually cause complete protection when given in the first four days of the incubation period, cause a sero-attenuated measles if given between the fourth and eighth days of the incubation period, but will be valueless thereafter.

On the other hand, if the dose of serum is increased as the incubation period progresses, the disease can still be prevented, even when serum is given late in the incubation period.

Although accurate comparative studies are not available, a study of the published results indicates that convalescent measles serum globulin from adult serum, and immune globulin from placental extract are probably comparable in potency. The dose generally recommended

is 2 cc for infants, 3 to 5 cc for young children up to the age of five years, and 5 to 10 cc over five years and for older children. Except for infants in whom complete protection is desirable, it is preferable to give the serum on the fifth to seventh days of the incubation period in an attempt to produce a sero-attenuated or modified measles which is followed by an active immunity.

Treatment—Measles is a disease which lends itself well to the study of the therapeutic value of a virus immune serum. First, measles convalescent serum is quite potent. Secondly, the disease can be accurately diagnosed and treatment instituted before it reaches its fastigium. It is astonishing that prior to 1936 it was believed almost universally that measles serum was without therapeutic value. Since then, several studies⁴ have established that the intravenous administration of large doses of convalescent serum (20 to 50 cc) during the pre-eruptive active stage would, in most instances, modify the disease. Such therapeutic effect has since been also demonstrated with the use of immune globulin by Stokes, Maris, and Gellis⁵ who also pointed out that such therapeutic modification was most clearly evident in those children in whom Koplik spots appeared earlier and, therefore, treatment was instituted earlier. They further report two instances of a temperature crisis and complete inhibition of the development of a rash despite the fact that, at the time of treatment, the disease was florid in character with severe cough and catarrhal signs.

POLIOMYELITIS

Prophylaxis—There are no clinical studies on the value of antiserum as a prophylactic measure. The low contagious incidence and the haphazard development of the recognizable disease makes such a study very difficult. However, there are sufficient laboratory studies to justify the belief that immune serum is effective prophylactically. Despite the difficulties in obtaining clear-cut evidence from experiments on monkeys, Schultz and Gebhardt's⁶ results are statistically significant indication of protection from the use of immune serum. Kramer,⁷ using the Lansing strain in mice and human convalescent serum, not only showed protection when serum was given up to two weeks before virus, but also demonstrated protection when serum was given *after* intracerebral virus infection, some protection being apparent even when given ninety-six hours later. He concluded that the protection appeared to be specific, due to absorbed circulating antibody and felt that there was some direct relationship between the amount of neutralizing antibody and the degree of protection. These results have been corroborated⁸ with the use of gamma globulin from adult serum wherein some protection was observed, even when the gamma globulin was given as long as ninety-six hours after intracerebral injection of virus in mice.

Treatment—Laboratory studies to determine the value of immune

antibodies in therapy are handicapped by the fact that such studies have not been done on animals in which the disease follows a course comparable to man. The necessity of producing the disease by intracerebral injection of the virus imposes a very critical test for the value of immune antibodies, particularly since hyperimmune antibody sources have not been developed. The inference may be drawn from the aforementioned work by Kramer and Stokes that there was therapeutic effect since protection was afforded to mice ninety-six hours after virus inoculation, for it is probable that after a ninety-six hour interval the injected virus had already invaded nervous tissue cells. However, none of the animals who showed symptoms or signs of active disease survived.

Critical analysis of the numerous clinical studies compels one to discount them all, whether favorable or unfavorable. From the introduc-

TABLE 2—TITRATION OF ANTIBODIES AGAINST THE LANSING STRAIN OF POLIOMYELITIS IN WHITE MICE

Serum Tested	Dilutions of Serum in Saline*					
	1/10	1/25	1/50	1/100	1/250	1/500
Human Convalescent Serum, Lot 115	0/6	2/7	2/5	3/8	4/8	6/6
Gamma Globulin	0/7	0/8	5/7	2/7	7/8	7/7
Normal Adult Serum, Lot 37	4/6	4/7	7/7	8/8	7/8	6/6
Normal Adult Serum, Lot 38	0/8	5/5	6/6	6/6	3/3	4/4
Control (Saline)	8/8			8/8		

* Numerator = number of mice dead

Denominator = number of mice inoculated

tory considerations, it is apparent that therapeutic efficacy is possible only from treatment instituted early in the course of illness, the so-called early paralytic stage. Even in outbreaks, early recognition is the exception rather than the rule. The course of the disease is variable and unpredictable, and statistically significant results would require rather large numbers of cases. Furthermore, there is no abundance of potent immune serum. The so-called "convalescent" serum is in most instances, serum collected from any paralytic patient, regardless of the interval since the illness. If the virus antibody titer of poliomyelitis blood behaves like that of other postinfectious antibodies, then most "convalescent poliomyelitis serum," used clinically, must have a relatively low titer of antibodies. In fact, some of the early titrations in monkeys, even though not too accurate, indicated that ordinary adult serum had as good a titer as the serum obtained from long-standing poliomyelitis patients.⁹ Recently we had occasion to

compare the titers of pooled adult serum, pooled convalescent serum obtained from patients who had had an attack of poliomyelitis from one to three years previously, and gamma globulin. These titrations, carried out against the Lansing strain of virus in white mice, revealed some very significant differences. Table 2 represents one such titration.

It appears from these titrations that the pooled serum from relatively recent patients is more potent than pooled adult serum and about equal in potency to gamma globulin. Clinical studies, therefore, in which relatively small doses (50 to 100 cc) of probably low potency serum was employed must be discounted.

The course of human poliomyelitis is another obstacle in attempts to establish the value of immune body therapy in this disease. When a diagnosis of early "nonparalytic" or "preparalytic" poliomyelitis is made, virus invasion of central nervous system cells has, in all probability, taken place. There is no way of knowing the extent of such involvement. If it is extensive at this time, obviously serum treatment cannot be very effective. The results of gamma globulin therapy⁸ in measles may serve as an analogy. The longer the interval between Koplik spots and rash (and, thus, immune therapy being instituted when fewer cells were involved) the more beneficial the effect. Our early diagnostic criteria for poliomyelitis are very limited and unsatisfactory. Until these criteria are improved, and until we establish a good method of making an early diagnosis before there is extensive nerve cell invasion, immune serum therapy in poliomyelitis will continue to labor under a handicap.

In a study* over a ten year period, comparatively large doses of convalescent serum (ranging from 100 to 800 cc and averaging 250 cc) have been administered to patients in the early acute stage without obvious clinical paralysis, the diagnosis being made after a careful history, physical and neuromuscular examination, and confirmed by positive spinal fluid findings. Attempts were made to secure this immune serum from as recent cases as possible, usually those occurring within one to five years. The serum was always administered intravenously, although in the first two years small amounts were also given intraspinally. The initial dose was 100 to 200 cc, depending on age and weight, and the same dose was repeated at twenty-four-hour intervals until convalescence set in. In this period of time, 298 patients were treated. The incidence of permanent paralysis was 23 per cent and the mortality was 1 per cent. Although there is no control group for comparison, it is felt that these results are clinically significant, because the clinical disease during this time was at least of average severity. From other reports,^{10a, 10b} it is reasonable to expect that 30 per cent of these early cases would have progressed to paralysis and that one third to one half of the 30 per

* This study was conducted from the Samuel Deutsch Serum Center, Chicago, by Doctor Albert M. Wolf and one of the authors.

cent,^{10b 10c} or 10 to 15 per cent, of the total number would have permanent paralysis. Thus, even though this study lacks a control group, the results are strongly indicative, for a much larger ratio of patients than normally expected had a more benign form of the disease when they received large doses of convalescent serum.

In this group of 298 preparalytic patients, thirty-two, or 11 per cent, subsequently developed definite signs of bulbar poliomyelitis. These patients were more acutely sick and consequently received more serum, the average therapeutic dose being 350 cc. Twenty of these patients at no time exhibited the fulminating and critical picture usually characteristic of bulbar poliomyelitis. Two of the thirty-two patients in addition to bulbar paralysis, also had spinal paralysis, in one mild, in the other moderately severe. There were two deaths in this group of patients with bulbar poliomyelitis, a significantly low fatality rate for this type of the disease.

MUMPS

Prophylaxis—Although the literature is not extensive, it is uniformly favorable on the prophylactic value of mumps convalescent serum. Since Hess¹¹ first used convalescent serum for this purpose, there have been other studies,¹² all reporting success with doses varying from 2 to 15 cc. In our experience, mumps convalescent serum confers protection on exposed susceptibles, but it does not appear to be a rich source of immune bodies. We believe that the minimum prophylactic dose should be 20 cc., and it would be wise to increase this amount to 40 cc. for adults.

Treatment—Mumps convalescent serum has been used in the treatment of acute, uncomplicated mumps in adults with the principal purpose of preventing extension of the disease, particularly to prevent orchitis in males. There are but few reports that merit consideration, those of De Lavergne and Florentin¹³ and Iverson¹⁴ are probably the best. Both these studies point to a reduced incidence of orchitis in patients who were given convalescent serum after the appearance of parotitis. De Lavergne and Florentin treated 113 patients with two doses totalling 30 cc. The contrast of 24 per cent orchitis in 107 untreated controls with 4 per cent in the treated patients is rather striking. Iverson administered 40 cc. of mumps convalescent serum to alternate cases in a group of soldiers with mumps. In the fifty-six serum-treated cases, 20 per cent developed orchitis, one bilateral, while in the fifty-six controls, 30 per cent developed orchitis of which three cases were bilateral. A recent study by Rambar¹⁵ yielded results comparable to those of Iverson. In view of the probable low immune body content of the serum (judging from the amounts required for effective prophylaxis) it appears that all these authors employed minimal and possibly inadequate amounts of serum. It would be worthwhile to conduct a study in which larger amounts of concentrated convales-

cent serum were used and to see if the complication rate could be consistently and significantly reduced

EQUINE ENCEPHALOMYELITIS

With improved and increased facilities for virus diagnosis, outbreaks of this disease are being recognized with increasing frequency. A large outbreak occurred in 1941, and 1080 cases in North Dakota alone were reported,¹⁶ with a mortality of 89 per cent. A smaller outbreak¹⁷ in Massachusetts in 1938 was highly fatal and caused about thirty deaths.

Prophylaxis—There is good laboratory evidence on the prophylactic value of hyperimmune rabbit and horse serum^{18, 19}. Small amounts of such serum will protect against subsequent intracerebral injection of many times the minimal lethal dose of virus.

Treatment—The principal evidence on the value of serum treatment of Western equine encephalomyelitis has been contributed by Zichus and Shaughnessy¹⁹ who worked with experimentally infected mice, guinea pigs and monkeys. It is significant that these workers rigidly observed those cardinal principles previously enumerated. Employing a laborious and prolonged course of immunization, they prepared a potent hyperimmune rabbit serum. Treatment was instituted as soon as the experimental animals became visibly sick. They gave large and repeated injections of serum, both intraperitoneal and intracardiac. With this regimen, 67.3 per cent of fifty-five guinea pigs recovered while only one of forty-one control animals spontaneously recovered. Further evidence that the serum-treated and recovered animals had passed through the active disease was subsequent resistance to lethal amounts of the live virus. Some of the recovered animals subsequently sacrificed showed histopathologic findings indicative of healing encephalomyelitis.

EPIDEMIC INFLUENZA

Laidlaw, Smith, Andrewes and Dunkin,²⁰ in 1935, reported experiments on the use of concentrated hyperimmune serum treatment in mice experimentally infected with influenza virus. Although treatment was instituted twenty-four and forty-eight hours after infection, only 35 per cent died, in contrast to 80 per cent fatality in control, untreated animals. Of the greatest significance was the observation that most of the treated survivors showed extensive lesions of the lungs when subsequently killed. This led these workers to state that this was "convincing evidence that the virus had reached and produced damage in the lungs, and that concentrated serum was powerful enough to arrest the pathological process."

These results have since been confirmed by Henle, Stokes and Shaw²¹. Not only was death prevented in experimentally infected mice up to forty-eight hours after infection when the animal was ill

with severe influenza, but Stokes³ states that serum treatment by the inhalation route required only about one-tenth that required by the intraperitoneal route for the same effect. This experience emphasizes the importance of having the immune antibodies at the site of infection. It also tends to confirm the favorable results reported by Smorodintsev²² who used convalescent serum treatment by inhalation of Type A epidemic influenza in man.

ATYPICAL PNEUMONIA

So-called "atypical" or "virus" pneumonia is being seen with increasing frequency. Although this disease is classified as a clinical syndrome, viruses have been isolated which fall in the psittacosis or ornithosis group. Meyer and Eddie,²³ in reviewing the literature, had expressed a favorable opinion on the value of convalescent serum in therapy of psittacosis, although they made the reservation that convalescent serum was of low potency and that better results should be expected from hyperimmune serum.

Solomon²⁴ found an opportunity, during an outbreak of "atypical" pneumonia at a Naval Air Station, to treat ten unselected patients with convalescent serum. He administered 250 cc. intravenously within three days of onset of illness, and reported crisis within twelve to eighteen hours following serum treatment, rapid recovery from illness, and discharge to duty after an average of twenty-two days. The control untreated patients usually recovered slowly, the temperature dropped by lysis, and they averaged thirty-nine days in the hospital before discharge to duty.

MISCELLANEOUS AND RELATED CONDITIONS

Isolated reports on a variety of conditions contribute to a constantly accumulating literature, all bearing on the value of immune serum in the treatment of intracellular parasites. Thus, Habel⁵ recently presented experimental data indicative of protective value in *antirabies* serum. Evans, Slavin and Berry²⁵ administered specific hyperimmune rabbit serum to mice experimentally infected with *herpes virus*. They showed a statistically significant effect from the serum even when it was administered forty-eight hours after infection. They concluded that antibody administration retarded, and in some cases arrested, progression of herpetic infection of the nervous system. In our laboratory,²⁷ hyperimmune monkey serum was employed in the treatment of mice infected intracerebrally with a virulent *lymphocytic choriomeningitis virus*. There was definite protection when serum was given as late as forty-eight hours after infection with 50 per cent of the animals surviving, while the fatality rate in the controls was 100 per cent.

Smorodintsev,²⁸ in a review on *spring-summer* . . . that convalescent or hyperimmunized animal

ing the incubation period provided the interval between injection of virus into mice and the inoculation of the serum was not greater than one to four days. Furthermore, he reports favorable results from use of the immune serum in treatment of the disease in man. He also stresses that, in order for therapy to be successful, the serum must be administered on the first or second day of the disease and followed by subsequent additional injections. He states unequivocally that "patients thus treated with repeated injections of convalescent serum showed a critical drop in temperature and a marked improvement of their general condition."

Topping²⁹ has reported clear-cut evidence that an immune serum containing large amounts of protective antibodies will save a large majority of guinea pigs infected with *Rocky Mountain spotted fever* when the serum is administered after onset of symptoms of the active disease. He³⁰ has also used the immune rabbit serum in treating fifty-two patients before the third day of rash. The fatality rate in this serum treated group was 3.8 per cent as compared to the expected rate of approximately 18.8 per cent.

There have been several reports on hyperimmune *typhus* serum. Wyckoff and Bohnel,³¹ in a recent study, demonstrated that hyperimmune rabbit antiserum "has a positive therapeutic effect in guinea pigs diseased with epidemic typhus" even when the serum is administered as long as five days following infection.

COMMENT

The chief aim in the presentation of material in this clinic is to open for review and reconsideration the value of immune bodies in the treatment of virus diseases, a topic which for long has been generally considered closed. The increasing knowledge on the behavior of viruses in the host and the accumulating favorable evidence justifies a reexamination of this subject and a possible reorientation of thinking.

In the light of our present information, the earlier failures and resultant hopeless attitude become clear. The field of virus research is relatively new, and rapid progress is still impeded by many difficulties. It was fundamentally important to use serums rich in antibodies. To produce such serums, potent antigens were necessary. It is only recently that any high-titered virus antigens have been prepared by isolating more virulent strains, by chick embryo technic, and by purification. The use of better antigens has made possible more potent serums which have been therapeutically successful where earlier efforts failed.

A very important qualifying factor in determining therapeutic efficacy of immune bodies is the extent of cell involvement at the time of therapy. At the present time, it appears that cells already parasitized by virus are probably beyond any help from serum therapy. Though cells may be invaded even before demonstrable signs and symptoms of

disease are present,³² there is no basis for the belief that cell involvement is extensive and complete early in the disease. In fact, all clinical evidence points to the usual course of virus illness as a progressively extending cell invasion. Maximal cell involvement probably takes place well after the active illness has become manifest. The introduction of immune bodies into the host and their presence at the location of infection should protect the healthy cells from invasion by virus. This must be the mechanism of therapeutic efficacy which has been so clearly demonstrated in a number of virus infections.

These considerations throw a sharp light on the great importance of early diagnosis of virus infections. At present, we are generally handicapped by vague diagnostic criteria. Differential diagnosis particularly is difficult. There are no specific laboratory tests to aid the clinicians to establish a definite early diagnosis. It is possible that this aspect of virus infections has been neglected because of the general attitude that therapy was worthless. We believe that an attitude of resignation is wrong. In fact, it is most important that a virus disease must be diagnosed at the earliest possible moment. Stokes⁸ has recently placed the greatest stress on the importance of earlier diagnosis. Clinicians and laboratory men should concentrate their efforts in establishing clear-cut diagnostic findings and laboratory tests.

Even though a serum is potent, and a relatively early diagnosis is made, it is still important that the serum be administered by a route that brings the immune bodies most rapidly to the seat of infection. The dose must also be adequate. Since the severity of many virus infections varies considerably, it would probably be a wise course to give maximal dosage rather than minimal.

It would be too much to expect that all virus diseases are susceptible to antiserum therapy. Those diseases against which potent serums can be prepared and which can be treated early should respond. It would also be too much to expect all patients to be treated successfully. Some virus infections, such as poliomyelitis, are extremely variable, and those patients with a fulminating disease and early extensive cell involvement by virus will not be susceptible to therapy.

The expression "too little and too late" can be aptly used to account for past failures in efforts to treat virus infections with immune serums. We should take cognizance of these mistakes in the future. We should renew our efforts to treat virus diseases in humans with immune bodies, following closely the cardinal principles of using potent serums, treating the patient early, and using adequate dosage by a route which will most rapidly bring the antibodies to the seat of infection.

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JAUNDICE IN THE NEWBORN

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JAUNDICE or icterus in the newborn is a symptom complex of a yellowish discoloration of the skin, mucous membranes, and fluids of the body, caused by an increase of bile pigments in the blood stream. All newborn infants have an abnormal amount of bile pigments in their blood but only about 30 per cent have this increased pigment to such an extent that it spills over into the skin and tissues as visible jaundice. There are many causes of hyperbilirubinemia, some of which are dangerous to the life of the child and require prompt treatment. It is our problem, therefore, when seeing a newborn infant with jaundice to attempt to differentiate the various pathological reasons for its occurrence.

Jaundice in the newborn may be classified into two groups, hemolytic jaundice in which a blood disturbance is the principal factor, and obstructive and infectious jaundice which principally involves the biliary system. The hemolytic group includes physiological jaundice or icterus neonatorum, icterus neonatorum precox, or prolonga, the symptom complex of erythroblastosis or hemolytic disease of the newborn, and various unexplained types of hemolysis that used to be grouped under the broad term of icterus gravis. The group considered as obstructive or infectious includes those caused by obstruction of the bile ducts, as in liver damage either infectious or congenital. This includes all types of antenatal and prenatal infection, Winckel's disease, syphilis and in the obstructive type, congenital atresia of the bile ducts.

ETIOLOGY

Icterus Neonatorum—This includes 98 per cent of all jaundice in the newborn and may be considered as physiological or a normal phenomenon. The cause of this jaundice is not entirely understood but the most accepted explanation is that a prenatal polycythemia which is due to the inefficiency of the placenta as a respiratory organ, and to the mixture of venous and arterial blood in the fetal circulation, is not needed after the birth of the child. As a consequence, when the lungs commence their function of oxygenation, there is a marked destruction of red cells with a liberation of hemoglobin. This hemoglobin is converted into hemobilirubin which the liver cannot successfully eliminate at this time. Bilirubin, therefore, appears in the blood stream of all newborn infants, and in certain individuals, in sufficient quantity to be deposited in the tissues.

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Other theories are that the liver of the newborn is not immediately capable of functioning as a mature organ in removing bilirubin from the blood stream, and Schick¹ believes that the hyperbilirubinemia is the iron-free part of the maternal hemoglobin, the maternal hemoglobin being broken up by the placenta to make iron available for the fetal hemoglobin. This would explain the more intense icterus of premature infants, as they are born when the placental iron metabolism is at its height. It is a common clinical observation that premature infants are always more severely jaundiced and for a longer period of time than full term infants, while overmature infants are relatively free of icterus.

Icterus Neonatorum Precox.—The older clinicians observed a small number of newborn infants in which jaundice was more intense than that of icterus neonatorum and lasted for a longer period of time. They termed these cases icterus neonatorum prolonga. Halbrecht,² in a study of 10,000 newborn babies, found sixty such infants. In 95 per cent of the cases he was able to demonstrate the incompatibility of the child's blood with that of the mother. He believed that the passage of anti-A and anti-B isoagglutinins from the mother to the child through the placenta hemolyzes the infant's red cells and produces an increase of bilirubin in the placental blood and later in the infant's blood stream.

Erythroblastosis Fetalis (Hemolytic Disease of the Newborn)—This condition is stated as occurring in one of every 200 newborn infants, but in my experience I have found it only in about one of 800 infants. I believe that the reason for this apparent discrepancy is that Rh-negative mothers are not evenly distributed among the population but occur considerably more in some localities than in others. The condition is presumed to be caused by the isoimmunization of the Rh-negative mother by an Rh-positive fetus, from an Rh-positive father. According to Levine,³ passage of the fetal blood across the placenta causes the Rh-negative mother's blood to form anti-Rh agglutinins, which pass back through the placenta and hemolyze the susceptible fetal Rh-positive blood.

In 90 per cent of these cases of erythroblastosis fetalis, the above conditions of an Rh-positive father, an Rh-negative mother, and an Rh-positive fetus are fulfilled. In the remaining instances the mother is Rh-positive or the baby is Rh-negative. Whether this is due to undiscovered agglutinins or to an entirely different pathogenesis is as yet unknown. Inasmuch as approximately 15 per cent of the white population is Rh-negative (Negroes, 5 per cent), the expected incidence of this phenomenon would be one seventh of all matings, and a much higher incidence than 1/500 full term deliveries would be expected. The reason for this variance is the tendency towards small families. The first baby is almost always immune, and a large proportion of the Rh-positive fathers are heterozygous. Only 50 per cent of

the offspring could immunize the mother. Even with a homozygous father, all the children may be normal even though Rh-positive if the Rh-negative mother is incapable of producing antibodies.

Nuclear Icterus—Whether this is a definite clinical entity or simply a complication of intense jaundice is not clear. It may exist alone or as a complication of hemolytic disease, infection, or biliary dysfunction. It is a rare condition, characterized pathologically by a deep yellow staining of the basal ganglia. Most observers agree that the primary factor is an injury to the nerve cells, with a secondary deposit of bile pigment. While intense jaundice always accompanies the disease, the degree of jaundice is not a cause of the condition. I observed an infant with erythroblastosis and an icterus index of 450 for eleven days, who did not develop the condition.

Unexplained Jaundice (Probably Due to Hemolysis)—There are instances in which the infant's symptoms clearly resemble hemolytic disease of the newborn when the mother is Rh-positive and the infant Rh-negative. There is no definite explanation for this. Proponents of the Rh theory believe that these instances may be due to atypical or indeterminable agglutinins, or to the agglutinins Hr, A or B. These constitute about 10 per cent of all instances of erythroblastosis or hemolytic disease. Infections either pre- or postnatal, congenital heart disease, or biliary dysfunction will occasionally cause jaundice, increase of young red cells in the blood, enlarged liver and spleen, anemia and other symptoms that are similar to erythroblastosis neonatorum or hemolytic disease of the newborn.

Sepsis—Almost any bacteria may cause the infection, the most frequent being the streptococcus, staphylococcus, pneumococcus and colon bacillus. Infection may occur prenatally or postnatally. The portal of entry is most often through the cord, and next the skin.

Winckel's Disease—This might be included under sepsis, although no definite organism has yet been found as a causative factor. It occurs late in the newborn period, and is very rare. It is characterized by jaundice, cyanosis and blood in the urine.

Congenital Syphilis—While not as common as formerly, this should always be considered. It can simulate every phase of erythroblastosis, sepsis or biliary dysfunction. It is usually seen if the mother has been untreated before the fifth month of pregnancy.

Obstructive Jaundice—This is due to congenital malformations of the bile ducts, and may be caused by almost any combination of atresia or stenosis. There is also some form of obstruction in sepsis but this is not considered under this heading. The obstruction to the entry of bile into the intestine causes an absence of stercobilin in the stools, and a high bilirubin content of the blood. As the disease continues, cirrhosis and enlargement of the liver and wasting of the child result.

SYMPTOMS AND COURSE

Icterus Neonatorum—This appears as a jaundice from twenty-four hours to four days after birth in an otherwise normal newborn. It varies from a slight discoloration of the sclera to an intense orange

TABLE 1—CLINICAL COURSE IN JAUNDICE IN NEWBORN

Hours of Life	Hemo-globin	Red Cells	Nucleated Red Cells	White Cells	Myelo-cytes	Clotting Time	Bleeding Time
<i>Erythroblastosis with Recovery</i>							
2 hr	25%	1,100,000	57,000	28,000	19%	5 min	30 min.
Transfusion 80 cc. A M. and 90 cc. P M.							
48 hr	58%	3,200,000	60,000	25,000	9%	5 min.	15 min
Transfusion 100 cc A M. and 80 cc P M.							
72 hr	65%	4,800,000	5 000	20,000	0	5 min	10 min
Transfusion 90 cc.							
96 hr	75%	5,000,000	0	15,000	0	5 min	6 min.
7 days	85%	5 000 000	0	13,000	0	5 min	6 min.
4 mos.	95%	5,500,000	0	16 000	0	5 min	6 min
<i>Erythroblastosis with Death</i>							
1 hr	38%	1,240,000	282 000	26,000	36%	6 min	1 hr
Transfusion 100 cc.							
12 hr	50%	1,800,000	132,000	16,500	30%	6 min	1 hr
Died at 16 hours.							
<i>Nuclear Icterus</i>							
Normal at birth, jaundice developed at 30 hours.							
48 hr	95%	4,800,000	0	9,200	6%	4 min	2 min
<i>Atresia of Bile Ducts with Erythroblastosis</i>							
2 hr	53%	1,600 000	162,000	42,000	10%	10 min	1 hr
Transfusion 80 cc.							
24 hr	77%	2,200,000	42,000	38,000	8%	10 min	1 hr
Transfusion 95 cc							
48 hr	95%	3,500,000	55 000	26,000	8%	12 min.	7 hr

color. It may deepen for a few days, fade during the next week, and entirely disappear in two weeks. The urine may be discolored with bile, but the stools are normal. The liver and spleen are not enlarged and the well-being of the child is not affected in any way. The blood is normal except for an increase of bilirubin of over 2 mg per 100 cc

(icterus index over 16) It must be remembered that the blood of the normal newborn infant may show as many as 5 per cent nucleated red cells during the first two days of life. These are normoblasts, but occasional erythroblasts are seen. There is no associated anemia, and the nucleated red cells decrease during this time.

Icterus Neonatorum Præcox.—In these infants the jaundice is a little deeper than in physiological jaundice, and may last for a longer period of time. The liver and spleen are not enlarged, and the well-being of the child is not affected in any way. The stools are normal but the urine may contain considerable urobilin. The blood will show an icterus index of over 20, and there may be nucleated red cells as high as 8 or 10 per cent. There may be a few erythroblasts and myelocytes. There is no associated anemia. Many of these cases are diagnosed as erythroblastosis neonatorum.

Erythroblastosis Neonatorum—Infants suffering from this condition or any variation thereof will show the following symptoms: jaundice, enlarged liver and spleen, an excess of nucleated red cells in the circulating blood, macrocytic hyperchromic anemia of varying intensity, and in cases of hydrops, edema of the tissues and body cavities. At autopsy an excessive number of erythroblastic foci are found throughout the body organs.

The initial symptoms vary from the extreme of so much edema that the fetus is born dead, or dies shortly after birth, to that of a jaundice that is only slightly more intense than that seen in physiological icterus neonatorum. In other instances the infant will show an anemia without the initial jaundice. The jaundice may be apparent at birth in the form of yellow vernix, or the infant may be born without visible jaundice, which appears and deepens almost under your eyes during the first twenty-four hours of life. During this period the spleen may not be palpable at birth but will enlarge to considerable size as the process develops. The liver soon becomes easily palpable.

The blood shows a macrocytic hyperchromic anemia in which the hemoglobin is reduced below 75 per cent and may be as low as 25 per cent, with the red cells below 3,000,000 and possibly below 1,000,000. There is an increase of nucleated red cells of from 10 to 50 per cent. The majority of these are normoblasts, the remainder erythroblasts. The white cells are increased, with numbers of myelocytes apparent. The platelets are decreased. In 90 per cent of these infants, the blood will be Rh-positive, while that of the mother will be Rh-negative and the father Rh-positive. Circulating antibodies will be found in about 60 per cent of the mother's blood but never in the infant's.

The urine usually contains bilirubin and the van den Bergh reaction gives a direct or biphasic reaction. The stools are rarely acholic and as much as the drop in red cells is not consistent with the degree of jaundice, there must be some degree of liver damage. The urobilin has been reported as lowered, and there are frequently

hemorrhages, melena or bleeding from the cord. The coagulation time is not usually increased, but the bleeding time is increased.

As the condition develops the child becomes more apathetic and listless, and with the deepening jaundice petechial and gross hemorrhages appear. Death usually occurs in the first forty-eight hours with cyanosis and collapse. When recovery takes place, the jaundice fades and the blood commences to regenerate. A few nucleated red cells may persist for several days. The urine continues to be bile-stained for some time. The liver and spleen may remain enlarged for several months. When recovery occurs in these children, they behave like any other infant, and there are no residual symptoms. Very infrequently nuclear icterus will develop in the first week. Such infants usually die, and if recovery takes place a hopeless idiocy is the result. Many infants who recover from erythroblastosis show a dark staining of the first teeth when they erupt. It does not seem to affect the second teeth, nor do the first show any other changes. These iron deposits appear to have occurred in fetal life.

Nuclear Icterus—This may develop with intense jaundice only, or during the course of an erythroblastosis, sepsis or biliary dysfunction. It is an uncommon condition. The jaundice is a deep bronzing, but as stated before, the degree of jaundice does not determine the disease. Associated with this are neurological symptoms of flaccidity, or spasticity and convulsions. It is usually fatal, death occurring in three or four days. In a child recently under my care, the birth was normal with no visible jaundice. Severe jaundice developed on the second day with flaccidity and apnea. Death occurred on the third day of life. The blood was normal, there were only 6 per cent of nucleated red cells, the van den Bergh test was indirect, and the icterus index was 100. Autopsy showed only the nuclear staining, with no evidence of increased erythropoiesis.

Sepsis.—In the prenatal type, the child is born with the following symptoms: jaundice, bleeding from the portal of entry (cord) or petechial hemorrhages, and enlarged liver and spleen. Frequently a positive blood culture can be obtained. In the postnatal type the symptoms are more likely to develop after the fourth day of life.

Winckel's Disease—This disease is characterized by the triad of icterus, cyanosis and hemoglobinuria. It is very uncommon at the present time. It usually begins in the later newborn period between the ages of four and twelve days of life, with a sudden onset of icterus which increases in intensity. Polyuria develops, and the urine is stained with blood pigment. Fever is not particularly common, but restlessness, cyanosis and rapid pulse and respiration occur. There is an increase of white cells, and an accompanying anemia. Death occurs in a few hours to two weeks.

Congenital Syphilis—Syphilis of congenital origin can simulate every phase of any of the above diseases. It is always best to obtain the

mother's Wassermann or Kahn reaction in any instances of intense jaundice, enlarged spleen, or anemia in the newborn, if it has not been done late in pregnancy. The infant's blood tests are not reliable during the newborn period. Roentgenograms of the child's long bones are more so. These will show the characteristic lessening in density at the epiphyses. However, it must be remembered that somewhat similar roentgenograms are occasionally found in erythroblastosis and in certain premature infants.

Malformation of the Bile Ducts.—Jaundice is the most striking symptom. It appears soon after birth and progressively increases until the skin becomes stained a deep green. In some instances the jaundice does not appear until one or two weeks after birth. The stools are white or clay-colored and contain fat. However, they may appear normal for several days due to the presence of meconium, or to an aberrant bile duct emptying into the bowel. The urine is highly colored and contains bile. The icterus index is high and the van den Bergh is direct. The liver and spleen enlarge as the condition progresses. At first there is no change in the blood but later an anemia develops. Strange to say, there is no change in the prothrombin content, or are there any hemorrhagic manifestations? While the condition develops in the newborn period, it may last for a considerable time. The child becomes greatly emaciated, and the liver becomes very large through cirrhoses.

I have seen an instance of congenital atresia of the bile ducts, as proved by autopsy, with all the symptoms of erythroblastosis, 25 per cent nucleated red cells, and increased areas of erythropoiesis. Other similar cases have been reported so that there may be some correlation between these two conditions. Davidsohn⁸ reports such a case which was explored and the ducts found patent. The child recovered following the operation. It would, therefore, be wise to treat such infants, with acholic stools but an excess of nucleated red cells with anemia, as erythroblastosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is shown in Table 2

PROGNOSIS

Icterus Neonatorum.—The patient always recovers.

Icterus Neonatorum Precox.—Recovery is the rule.

Erythroblastosis Fetalis.—The mortality is given as 50 per cent. However, this can be split into the following. Infants born with edema or jaundice almost always die. Infants with jaundice developing after birth almost always live with treatment. Our mortality is 10 per cent. If death occurs, it is usually within four days. Infants born with anemia always recover.

Nuclear Icterus—Infants with this affection almost always die. If they do live, the result is idiocy.

Sepsis—Prenatal sepsis is almost always fatal. With treatment the prognosis of postnatal sepsis is good.

TABLE 2—DIFFERENTIAL DIAGNOSIS

Type	Age of Onset	Skin	Liver and Spleen	Urine	van den Bergh	Icterus Index	Blood
Icterus neonatorum	2-6 days	Golden yellow	0	Urobilin	Indirect	16+	Nucleated red cells not over 5%. Occasional erythroblasts.
Icterus neonatorum precox	2-6 days	Deep yellow	0	Urobilin	Indirect	20+	Nucleated red cells not over 8%. Occasional erythroblasts.
Erythroblastosis fetalis	Birth to 48 hr	Deep yellow to bronze. May be paler early or later. Petechiae.	Enlarged	Urobilin Bilirubin	Biphasic	75+	Nucleated red cells 20 to 50%. Many erythroblasts. Myeloblasts. Macrocytic hypochromic anemia. In 90% infant will be Rh positive, mother Rh negative, father Rh positive.
Nuclear icterus	24 to 48 hr	Deep yellow	0	Urobilin	Indirect	75+	No change if occurs alone. If with erythroblastosis—like above.
Sepsis	After 4th day unless prenatal	Yellow. Petechiae. Gross hemorrhage.	Enlarged	Normal or urobilin		16+	Nucleated red cells may be over 5%. Anemia develops. Increased white cells.
Winckel's disease	4-12 days	Deep yellow. Cyanosis.	0	Blood. Urobilin	Indirect	75+	Increased white cells. Anemia may develop.
Congenital syphilis	Any time	Varying jaundice. Skin lesions.	Enlarged	Urobilin Bilirubin	Biphasic	16+	Can simulate erythroblastosis. Positive Wassermann Kahn.
Congenital heart disease	Birth to 14 days	Some jaundice. Usually more cyanosis.	Enlarged	Urobilin	Indirect	16+	Nucleated red cells can run over 10 per cent. Usually normal red count or polycythemia.
Atresia of bile ducts	Birth to 14 days	Jaundice increases to deep green.	Enlarged	Bilirubin. Clay stools.	Direct	100+	Usually no change. May have nucleated red cells over 10%.

Winckel's Disease—Although formerly considered fatal, the prognosis is now good, with treatment.

Congenital Syphilis—The prognosis is good, if the disease is treated at once.

Congenital Atresia of the Bile Ducts—The prognosis is not good. Occasionally it can be treated surgically but if inoperable, the pa-

tients usually die in the first year, although some have lived past five years

TREATMENT

Icterus Neonatorum.—No change in the normal newborn procedure is justified or necessary

Icterus Neonatorum Precox.—Same as above.

Erythroblastosis Fetalis.—Immediate treatment is required. Probably no condition in pediatrics will respond so rapidly to the proper treatment. The life of the child depends on the rapidity of the transfusion. The diagnosis may be evident at birth in a large, boggy placenta, golden yellow vernix, green amniotic fluid, and edema, jaundice or pallor of the child. In such instances, an examination of the cord blood should be done immediately. If a macrocytic hyperchromic anemia is found (red cells under 4,500,000, hemoglobin less than 75 per cent), with nucleated red cells over 8 per cent, a transfusion of compatible blood should be given at once. The blood of the mother should never be used, and it is just as well not to use that of the father. I do not wish to confuse the reader. All of the latest reports on the treatment of this condition emphasize the necessity of transfusing the infant with Rh-negative blood, the inference being that the transfusion of Rh-positive blood is not only useless, but is dangerous to the life of the child. I think that these statements are very unfortunate. I have seen instances of desperate attempts to obtain Rh-negative blood, while the child suffered from a lack of transfusion of any blood. I believe that no physician need feel that he has endangered the life of the child by not giving Rh-negative blood, because in the majority of instances it makes little difference whether Rh-negative or Rh-positive blood is transfused. For the past fifteen years I have given these infants any blood that did not agglutinate the cells and serum of the infant after incubation at 37° C for one hour and centrifugation at 600 revolutions per minute.

Some infants will require only one or two transfusions, while others may need many more. In one instance I found it necessary to give an infant twenty-five transfusions. These may be given twice a day until the child is out of danger. In some instances the child does not respond well to the transfusions, the jaundice deepens, and the anemia continues. In such cases the donor should be changed. I have found that some of these cases respond to Rh-negative blood and others do not. In one instance we used eight donors, some Rh-negative, before we found one that helped the child. This A₁ Rh-positive infant had cold agglutinins to seven A₁ Rh-negative and Rh-positive donors.

Almost as important as the transfusions is the necessity of supplying oxygen. These infants should be placed under an oxygen hood and given three to four liters per minute as long as nucleated red cells are present in the blood smear, or as long as there is clinically any sign of cyanosis. Afterwards, as the jaundice persists, it should be given fifteen minutes out of every two hours.

The nutrition of the child is obviously of importance. Feedings can be begun at once of pooled breast milk, or any good, easily digested food. The mother's own milk should never be used as there is evidence that the antigens are transmitted through it. Usually the child can take a bottle, or if not, a dropper or tube can be used. If there is any question of dehydration or lack of ability to take food, the child can be given 80 to 100 cc of 5 per cent glucose in normal saline once or twice a day. This may be given through the cannula, if left in place, or if not, subcutaneously. Darrow⁶ believes that this is specific to combat liver damage.

It is customary to give some form of vitamin K or calcium to these infants, as they frequently show some hemorrhagic disturbance. The supposition is that they have a prothrombin deficiency. Actually they are deficient in platelets, and it is unnecessary to give vitamin K or calcium if ample transfusions are given, as they furnish enough of both elements. It must also be remembered that many of these infants die of infection, so every effort should be made to guard them from this hazard. If any type of infection develops, I have found that it is not dangerous to give one of the sulfonamide drugs in full doses of 1 to 2 grains per pound body weight. However, since the advent of penicillin we have given 10,000 units subcutaneously every three hours until the infection subsided.

Nuclear Icterus—The treatment is similar to that of erythroblastosis fetalis.

Unexplained Jaundice of Hemolytic Origin.—Same as above.

Sepsis—Transfusions of typed blood are given intravenously, 10 to 15 cc per pound body weight. Sulfadiazine or any of the other sulfonamides, 1 to 2 grains per pound body weight by mouth, or penicillin, 10,000 units every three hours subcutaneously, may be given. Support the infant by pumped breast milk or any easily digested food, feed

by tube or dropper if swallowing is difficult. In liver involvement, give 100 to 150 cc of 5 per cent dextrose in normal saline, intravenously or subcutaneously, once or twice daily. In liver involvement with cord hemorrhage or petechiae, give some form of vitamin K by mouth or hypodermically if desired, 5 mg per day. This will react in two hours.

Congenital Syphilis—Begin by giving a 25 mg (half 50 mg) tablet of acetarsone by mouth every other day and increase the amount to 50 mg daily after a week. It is also possible to give 18,000 units of penicillin⁷ per pound of body weight in twenty-four hours, giving it every four hours for a week.

Winckel's Disease—Give intravenous transfusions of 10 to 15 cc. of citrated whole blood per pound of body weight immediately. This should be repeated at least daily as long as the cyanotic condition continues. Also give one hundred cubic centimeters of 5 per cent dextrose in normal saline intravenously or subcutaneously once or twice daily. Continue giving oxygen as long as cyanosis lasts.⁸

Congenital Atresia of Bile Ducts—Give the infant easily digested, high protein food such as breast milk, or lactic acid milk. An exploratory operation should be done as soon as the diagnosis is established. There is usually no hurry about this, any time in the first two or three weeks being satisfactory. Build up the child for operation with one or two transfusions of citrated whole blood, 10 to 15 cc per pound of body weight. Also give 100 cc of 5 per cent dextrose in normal saline, intravenously or subcutaneously as necessary for dehydration. It is not necessary to give vitamin K or bile salts before operation. If these children are found to be inoperable on exploration, they may continue living in many cases. Instances have been reported of such children living as long as four years.

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THE ANEMIAS OF CHILDHOOD

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ALTHOUGH the mechanism of anemia in infancy and childhood is the same as that of the adult it differs in its manifestations, primarily because of the lability of the blood-forming organs of the child. Anemia is the result of (1) failure of production of normal red cells, or (2) loss of blood, or (3) destruction of cells.

ANEMIAS DUE TO DEFECTIVE BLOOD FORMATION

The hematopoietic tissue of the infant is immature, and does not assume all of its adult characteristics until the age of 12 or 14 years. The distribution of erythropoietic centers at birth extends throughout the marrow of all of the bones of the body, and also in extramedullary deposits in the liver, spleen and lymphatic tissues. Shortly after birth the marrow assumes the load of erythropoietic activity (although the extramedullary centers may be called into activity in times of stress), and by the age of 3 years the red marrow of the long bones of the lower extremities gradually becomes pink as fat replaces marrow in the center of the shaft. By the age of 12 to 14 years the distribution of red marrow is similar to that of the adult, and is limited to the distal ends of long bones and to the flat bones of the skull and skeleton. The maturation of red cells in the marrow requires a supply of certain elements—iron, copper, vitamin C, thyroxin, the intrinsic factor present in gastric juice and vitamin B, and proteins—all of which are supplied to the normal infant in gestation through the maternal blood. The normal infant as well as the premature infant born of a normal mother who shows no degree of anemia has sufficient stores of iron to prevent the development of anemia throughout the first six to eight months of life.

Physiological Anemia of the Newborn—The normal full term infant shows at birth a polycythemia due to the low oxygen tension of fetal circulation, the red blood cell count varies from 4,800,000 to 6,200,000 per cu mm and the hemoglobin from 18 to 23 gm on the first day of life, and a few reticulocytes and nucleated red blood cells are present. As the adjustment to atmospheric oxygen tension is made, the polycythemia disappears and the red blood cell and hemoglobin values drop to 4,200,000 to 5,300,000 per cu mm and 15 to 20 gm, respectively, the reticulocytes disappear by the end of the second

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week This adjustment is accomplished by destruction of erythrocytes in the circulation and is accompanied by a physiological icterus of skin and sclerae (icterus neonatorum) and an increased output of urobilin in the stools The drop in red blood cell count continues and reaches a low point at 6 to 8 weeks of life with a red blood cell count of 3,400,000 to 4,400,000 per cu mm and hemoglobin values of 11 to 14 gm, this fall constitutes a physiological anemia which recovers spontaneously by the end of the first year During the period of rapid decline in the red count, reticulocytes are absent, but return spontaneously by the end of the second month Administration of iron is without effect in the prevention of the anemia, the anemia is normocytic and normochromic except during the early recovery phase when their diameter may be increased temporarily

Premature infants may show an anemia which is an exaggeration of the physiological anemia and a reflexion of the lability of immature organs of hematopoiesis The anemia is usually apparent by the end of the third month and its severity varies in proportion to the degree of prematurity Recovery begins by the third month and is usually complete by the seventh month The premature is not necessarily lacking in supply of iron in proportion to body weight, but as the rate of body growth exceeds the demand of the normal infant, the supply may be inadequate for normal, spontaneous recovery and an iron deficiency may result in a true iron deficiency anemia unless medicinal iron is supplied As a prophylaxis for the development of the iron deficiency which may follow the physiological anemia of the premature, ferrous sulfate gr II to gr IV is advisable after the third month

Nutritional Anemias—Iron deficiency anemia, which is always characterized by microcytosis and hypochromia, may be seen in infants after the fourth month of life and also later in childhood It is seen in (1) babies under 1 year of age born of anemic mothers, (2) prematures and twins whose iron stores are inadequate for the rate of growth, (3) infants and children subjected to repeated infections, (4) infants and children suffering chronic blood loss, and (5) babies who continue an exclusive milk diet past the sixth month of life Recovery from the deficiency may be expected within six weeks with adequate iron therapy

Nutritional anemia is not necessarily due only to an iron deficit as it is usually associated with *vitamin deficiencies* and with other factors related to poor hygiene The anemia which occurs in chronic disorders of the bowel, such as celiac disease and fibrocystic disease of the pancreas, is a nutritional type of anemia and is dependent upon failure of the bowel to absorb the necessary building stones In most instances the *anemia of celiac disease* is of the iron deficiency type, microcytic and hypochromic, rarely it is macrocytic and hyperchromic, and responds to liver therapy Anemia in childhood *scurvy*

is rare unless hemorrhages result in blood loss, and the chronic anemia seen in adults with the subacute form of the disease which responds to vitamin C therapy is seldom seen.

Anemias due to infection may be a true iron deficiency type as the appetite lessens and the intake of iron is decreased, or may be due to failure of absorption of iron when bowel function is impaired and as the excretion of iron is hastened. The ordinary infections of childhood—the acute exanthemas and respiratory infections—are rarely accompanied by a severe anemia, but certain infections, particularly pneumonia, scarlet fever, pyelitis, typhoid, sepsis, streptococcal infections, osteomyelitis and syphilis may be accompanied by severe anemia. In addition to the iron deficiency there may be a destructive process per se with either impairment to normal production of red cells due to the action of toxin on bone marrow or destruction of circulating cells. It has been shown that resistance to infection is diminished in the presence of anemia, and that prevention of iron deficiency anemia in early childhood reduces the incidence of intercurrent infections.

Von Jaksch's anemia (pseudoleukemia infantum) is an anemia described in the older pediatric literature characterized by severe anemia developing in infants between 6 and 12 months of age, associated with splenomegaly and leukocytosis and the presence of immature white cells and normoblasts. This condition is no longer considered as a clinical entity, but as a common symptom complex caused by various factors and accompanied by some degree of nutritional anemia. Some clinicians (Parsons) consider it to be a subacute hemolytic anemia of unknown etiology.

The *chlorotic type of anemia* described in older pediatric literature and seldom seen in recent years was an anemia which developed in adolescence and was characterized by marked pallor of greenish tinge and marked hypochromia, and was an example of severe nutritional anemia probably associated with blood loss.

Aplastic Anemia—Aplastic anemia in which all the formed elements of the blood are diminished may be congenital or acquired. The congenital type is rare. The anemia is seen to develop about the third month at which time the infant develops a progressively severe anemia accompanied later by hemorrhagic tendencies, leukopenia and thrombopenia. Study of the marrow may show a fatty marrow depleted of all cells, or a marrow which is histologically normal but functionally ineffective, in the latter instance a marrow block is said to exist. The prognosis is grave. The acquired type may be the result of sepsis, other infections, or toxins—exogenous or endogenous—or to chemicals such as benzol, arsphenamine or the sulfonamides, or to malignant growths leukemia, or x-ray or radium therapy. The course is rapid and the prognosis grave. Treatment consists of repeated transfusions. The prognosis of the acquired type is also grave and depend-

ent upon the degree of bone marrow damage and upon the etiologic agent. Recovery may follow repeated transfusions, liver extract, and pentnucleotide bone marrow therapy. Stimulating doses of x-ray have been used to advantage but only when the bone marrow is not aplastic.

Chronic Hypoplastic Anemia—A more common type of anemia is chronic hypoplastic anemia in which only the erythropoietic elements are affected. These cases are also rare but have been reported in several pediatric clinics. The anemia is characterized by an absolute reduction in the total number of red cells which retain their normal size and hemoglobin content together with marked reduction in reticulocyte count, leukopenia of 4,000 to 6,000, and a normal blood count. Repeated transfusions are required and recovery may occur after months or years of transfusions and liver extract, iron and vitamin therapy.

ANEMIAS RESULTING FROM LOSS OF BLOOD

Anemia resulting from rapid blood loss, following hemorrhage for any cause, may be fatal when a loss amounting to one-third of the blood volume occurs within a short time, whereas a loss of two-thirds of the blood volume over a twenty-four hour period may be tolerated without serious consequences. The acute hemorrhage incident to the hemorrhagic diathesis, thrombocytopenic purpura, hemophilia, rupture of an esophageal varix in congestive splenomegaly, and hemorrhagic disease of the newborn may call for immediate replacement of blood by transfusion. In contrast to the urgent need for borrowed blood, is the striking tolerance to the chronic anemia resulting from blood lost in small quantities over a long period of time and which occurs in the more subacute forms of purpura, hemophilia, ulcerative colitis, and parasitic infections of the bowel.

HEMOLYTIC ANEMIAS

The destruction of blood elements by hemolysis results in a type of anemia which is designated as *hemolytic*, and which has certain characteristic features. The excessive destruction of red cells is accomplished by hemolysis of the cell, with or without destruction of the cell membrane, pigment is released with the plasma, and an excessive amount is excreted in the urine and stools. The excessive destruction of red cells results in a hyperplasia of the bone marrow which may expand at the expense of the bony cortex. The demand for new cells in the blood is met by the release of large numbers of reticulocytes by the marrow, and more immature and even defective cells may be produced and released. The common findings in individuals showing a hemolytic anemia are (1) anemia, (2) jaundice of an acholuric type, splenomegaly, bilirubinemia, reticulocytosis, great variation in size, shape and staining qualities of the erythrocytes, an elevated icteric

index, an indirectly positive van den Bergh test, and increased excretion of urobilinogen.

Hemolytic anemia may be caused by *toxins*, bacterial or chemical, by *hemolysins*, disorders which produce a hemoglobinuria, or by *constitutional factors*. Of these anemias, brief mention will be made of those commonly seen in childhood.

Of the hemolytic anemias resulting from *toxins*, the most common one seen in childhood is seen in sepsis due to streptococcal infections. The hemolytic process affecting the erythrocyte is usually accompanied by a fragmentation of the cells, and a profound effect on the bone marrow which may result in either a marked reduction in the number of leukocytes and blood platelets, or conversely in a marked leukocytosis with the outpouring of immature granulocytes. The *chemicals* responsible for the hemolytic reaction in childhood are most commonly lead, one of the sulfonamides, or one of the arsenicals.

There are four clinical entities among the hemolytic anemias which merit more detailed discussion: (1) the acute hemolytic anemia of Lederer, (2) hemolytic anemia of the newborn, and (3) the constitutional hemolytic anemias, namely (a) Mediterranean anemia, (b) sickle cell anemia, (c) congenital hemolytic anemia.

Acute Hemolytic Anemia of Lederer.—The acute form of hemolytic anemia was described in 1925 by Lederer and similar cases have subsequently been described by Parsons, Wiggs and other investigators. The illness starts with a sudden onset of fever, abdominal pain and jaundice, with rapidly increasing pallor and signs of acute blood loss, dyspnea, tachycardia and syncope. The blood shows leukocytosis and marked anemia with reticulocytosis and hemoglobinemia, there may be a hemoglobinuria. The van den Bergh test is indirectly positive. Evidence of sepsis is lacking, although Lederer felt an unidentified infection might be a factor. The patient is critically ill and dramatic improvement is obtained by transfusions. A subacute, more chronic form of hemolytic anemia of similar type is not uncommon, and in these cases spontaneous recovery may occur. Although the etiology is unknown the clinical entity seems to be established.

Erythroblastosis Fetalis.—Hemolytic disease of the newborn, or erythroblastosis fetalis, is a familial disease occurring late in fetal life, or shortly after birth, in which excessive destruction of the erythrocytes takes place in the bone marrow, liver and spleen, together with marked hyperplasia of the erythroblastic centers and erythroblastemia. This disease rarely develops in the first pregnancy and is more commonly seen in the second or third child as the mother becomes sensitized by repeated pregnancies. Other synonyms for this condition are universal edema of the newborn, familial icterus gravis and congenital anemia. The mechanism of the hemolytic process has been shown by Levine and co-workers (1941) to be caused by an anti-Rh agglutinin, present in the mother's blood and transmitted to the fetus, and which hemo-

lizes the infant's erythrocytes. These agglutinins are demonstrable in about 30 per cent of mothers bearing children with the disease. The blood of the fathers of these children contains the Rh factor. The child's blood contains the factor. In the mother's blood the factor is absent. Instances have occurred in which the disease has developed in children of mothers with Rh-positive blood. In these infants rare types of anti-Rh agglutinins have been demonstrated.

The Rh factor is inherited as a dominant trait and consists of many subgroups. It exists in about 85 per cent of the total population and is absent in 15 per cent. Individuals whose blood contains the factor are designated as Rh positive, those who fail to have it are designated as Rh negative. Ninety per cent of the mothers of children who develop hemolytic disease of the newborn have been shown to be Rh negative. The remaining 10 per cent of mothers whose blood is Rh positive and who give birth to children with the disease have been shown to have other agglutinins incompatible with the infant's blood. Erythroblastosis fetalis occurs in approximately 1 in every 200 births, although the mating of Rh-positive fathers and Rh-negative mothers occurs in about 11 out of 100 matings. The low incidence of the disease in proportion to the high frequency of these matings may be explained by (a) failure of the Rh elements in the fetal blood to enter the maternal circulation, (b) failure of the mother to produce the anti-Rh agglutinins.

The infant may be born dead, may show hydrops fetalis and die shortly thereafter, or may be deeply jaundiced with enlargement of the spleen and may rapidly develop a hemolytic type of anemia which is progressive during the first twenty-four hours. The infant may show no jaundice at birth but become jaundiced during the first twelve hours, and the anemia may not develop until the second or third day or reach its height before the first week. Ominous symptoms are lassitude and lethargy. The blood shows marked reduction in the red count and hemoglobin, a reticulocytosis, and large numbers of erythroblasts which usually disappear within the first forty-eight hours. The van den Bergh sign is positive and the icterus index is elevated. There may be thrombopenia and prolonged prothrombin time with hemorrhagic diathesis. The stools show increased excretion of urobilin and may be acholic between the fifth and twelfth days.

In mild cases the disease may be self-limited, in which case a reticulocytosis develops by the fourth to sixth week and the blood becomes normal by the fourth month. In a certain number of cases, even though the degree of icterus may not be severe, the basal ganglia may be damaged and become deeply bile stained. When this occurs some degree of cerebral damage may be expected, with subsequent mental deficiency and spastic diplegia. This condition is known as kernicterus.

In erythroblastosis fetalis the anemia is usually sufficiently severe to warrant transfusion, and Rh-negative blood should be given if avail-

able. If not available, Rh-positive cells may be separated from plasma containing the agglutinins and the cells suspended in normal saline to reconstitute the normal hematocrit. Transfusions of 10 to 15 cc per pound of body weight should be given as frequently as necessary to keep the red blood cell count above 2 million. It has been shown that the presence of the mother's Rh positive agglutinins in the fetal blood will hemolyze cells of the Rh-positive donor within a few days and increase the hemolytic process, whereas cells of Rh-negative donors are not destroyed and remain in the fetal circulation as long as ninety days. Therefore a more prolonged benefit can be expected from Rh-negative blood transfusions. If the child survives during the neonatal period the prognosis is good, barring the occurrence of kernicterus. After the first month persistence of the hemolytic process is rare although a hemorrhagic tendency may develop.

Mediterranean Anemia—Mediterranean anemia is a grave and progressive disease characterized by anemia, splenomegaly and bone changes, which occurs almost exclusively in children of races inhabiting the borders of the Mediterranean. It is a congenital and hereditary disease which often affects several children in a family. The cause is a defect in hematopoiesis the nature of which is unknown. The associated pathology is shown to be a hyperactive bone marrow which produces an abnormal erythrocyte which is destroyed by a process of fragmentation. The degree of hemolysis, as evidenced by the presence of bilirubinemia, is less marked in this disease than in the other hemolytic anemias also the evidence of fragmentation of the red cell is more prominent. The hyperactive marrow results in widening of the marrow space at the expense of the cortex of all of the bones of the body, especially those of the skull, producing typical x-ray changes and widening of the malar and temporal bones of the face. The presenting symptoms are commonly those of enlargement of the abdomen and increasing pallor noticed by the parents when the child is three to four years of age. The disease is seldom noticed in patients under 1 year of age unless it has occurred in other members of the family and the parents are alert to the symptoms. It has been recognized, however, as early as 4 weeks of age.

The course is chronic and characterized by repeated infections and chronic debility secondary to the anemia. Growth and stature are retarded. With increasing age the facial characteristics become more prominent with widening of the malar bones, flattening of the orbit, and prominence of the maxillary ridges which together with the subicteric tint of the skin produce a mongoloid facies. It is a common observation to one who sees many of these patients that they all look alike. Although the skin obtains a subicteric tint, icterus of the sclera is less marked than in other hemolytic anemias. There is progressive enlargement of the spleen. The disease is often fatal when it develops at an early age, and few live beyond the tenth year of life although

occasionally patients with milder forms of the disease are known to live into adult life

The anemia is profound. In severe cases the red count ranges around 1 million and in less severe cases $2\frac{1}{2}$ to 3 million. Hemoglobin values vary from 3 to 8 gm. The red cells show marked anisocytosis, varying from large macrocytes to microcytes. In spite of the presence of macrocytes the cell volume is low due to the thinness of the cells and the increase of microcytes and fragmented erythrocytes. In addition to marked change in size there is marked variation in shape with fragmented forms of both nucleated and nonnucleated red cells. A characteristic feature is the irregular distribution of hemoglobin. Large numbers of erythroblasts of all ages are present. The percentage of nucleated red cells increases after splenectomy and remains elevated in contrast to the reduction in the number of normoblasts following splenectomy in hemolytic anemia. The other formed elements of the blood are unaffected. The urine shows increased urobilin and urobilinogen. The icterus index is slightly elevated (15 to 30). There is no effective treatment for the disease.

Sickle Cell Anemia.—Sickle cell anemia is a hereditary and congenital disease of the hematopoietic system which occurs entirely in Negroes and in other races only when an admixture of Negro blood has occurred. The typical feature of the disease is the production of abnormal erythrocytes which assume a sickle or crescent shape in an environment of anoxia, either *in vivo* or *in vitro*, and which are hemolyzed under certain conditions with resultant anemia. The sickling trait is widely prevalent in the Negro race, occurring in 7 to 10 per cent of the Negro population. Figures recently collected from the canal zone indicate a similar incidence of the trait in brown, black and mestizo peoples of that region. The incidence of the disease sickle cell anemia is reported variously as 2.5 to 9 per cent of those individuals who possess the sickling trait, and as less than 1 per cent of the entire Negro population. No hemolytic process is demonstrable in individuals who show no signs of the disease. The chronic hemolytic process in individuals with the disease is evidenced by varying degrees of virulence of the disorder.

In children the disease may be manifested in infancy, but usually does not become apparent until the second or third year of life. The common symptoms are related to the chronic anemia—weakness, fatigue and pallor—and the occurrence of hemolytic crises, which are usually accompanied by fever, abdominal pain and vomiting. These symptoms may be due to infarcts of the spleen, which occur commonly, and may be confused with those of acute appendicitis. The spleen is enlarged, the pallor of the mucous membranes is obvious, the sclerae are icteric, and hemic murmurs may be present. Joint pains and ulcers of the legs, of common occurrence in adults with the disease, are rare in children.

The anemia is of variable degree in individual cases ranging from a chronically severe anemia with red blood cell count below 2 million to a mild anemia with counts of 3 to 4 million. The anemia is of the hypochromic type. Reticulocytes are constantly present and following a hemolytic crisis large numbers of normoblasts are seen. The leukocyte count is moderately elevated, the platelets are normal between attacks, and following crises a marked leukocytosis and elevation of the platelet count occurs. The icterus index is chronically elevated, the van den Bergh test is positive, and the fragility of the red blood cells is slightly increased. The sickling trait can be demonstrated in wet smears in which the film is protected from air by a sealing of oil, or by replacement of air by carbon dioxide. The urine and feces show an excessive excretion of urobilinogen which is exaggerated during a crisis. The bone marrow is chronically hyperplastic, and in some individuals characteristic x-ray findings common to all the hemolytic anemias, thinning of the cortex, generalized osteoporosis and radial striae of the skull, may be seen.

Supportive treatment for the anemia is indicated—iron, liver extract, and general measures for the control of a diet adequate in protein and vitamins. Transfusions are necessary after severe crises. In severe cases with frequent crises splenectomy may be indicated although it has no effect in removing the essential cause of the disease. The chronic hemolytic process is compensated by the constant production of new erythrocytes which are delivered to the blood as reticulocytes and result in a chronically hyperplastic bone marrow. At intervals hemolytic crises occur when large numbers of cells are destroyed and the marrow responds by the release of normoblasts and granulocytes into the peripheral blood.

The degree of the hemolytic process varies widely in different individuals. The condition of microsplenectasis may exist in members of affected families—without signs of a hemolytic process—a subacute process in which the only symptoms are those of a chronic mild anemia, a subicteric tint of the skin and sclera, and splenomegaly, hemolytic crises may never occur, or the first crisis may occur late in adult life. The virulence of the disease is increased by transmission—a mother showing a mild form may give birth to a child with severe manifestations. The disease is encountered rarely in the newborn and is seen with progressive frequency in childhood and young adult life. In its severe form in childhood the symptoms are commonly recognized by the occurrence of a hemolytic crisis in which there is a sudden onset of fever, abdominal pain, increasing jaundice, and anemia.

Chronic Hemolytic Anemia—Chronic hemolytic anemia, known variously as acholuric jaundice, hemolytic icterus, or Minkowski-Chauffard's disease, is a familial disease whose chief symptoms are an acholuric jaundice associated with anemia of a hemolytic type, splenomegaly, and recurrent hemolytic crises. The erythrocytes are defec-

tive, they are spheroidal instead of normally biconcave and disk shaped. The diameter of the rounded cell is less than normal, these microspherocytes are more than normally fragile, the increased fragility is demonstrated through greater susceptibility to hemolysis in hypotonic saline. The cause of the production of defective erythrocytes is a moot question, microspherocytosis is a constant finding in the disease, and present after splenectomy, although the anemia is cured by the procedure. Whether it is due to an inherent defect in the hematopoietic tissue, or whether it is caused by the presence of an inherited hemolytic agent that produces the initial swelling and change in shape of the cells rendering them more susceptible to hemolysis is unknown.

The clinical course is characterized by a severe hemolytic crises, in which the red blood cell count may drop below 1 million and the hemoglobin to 3 to 5 gm. The leukocytes are elevated to 30,000 to 50,000. The marrow response is characteristically that of an outpouring of large numbers of reticulocytes which may reach 50 to 95 per cent of the red cells, normoblasts are commonly seen, although more immature nucleated red cell forms are rare. The erythrocytes have a cell diameter of 5 to 6 microns, although the volume index is normal or slightly reduced. Since the cells are thicker than normal the increased fragility of red blood cells to hypotonic saline is demonstrable, hemolysis begins at 0.48 per cent and is complete at 0.42 per cent, whereas in normal blood it begins at 0.42 and is complete at 0.34 per cent saline. The other laboratory findings are an elevated icterus index, indirect van den Bergh, bilirubinemia and increased urobilin in the stools.

Treatment consists of supportive measures to the anemia between attacks and removal of the spleen if the severity of the disease indicates it. Splenectomy is best performed between attacks although some authorities feel that in severe cases it is justified during attacks. It is noteworthy that these patients are susceptible to reaction when blood transfusions are necessary during an attack and that special care is necessary in assuring the use of compatible blood.

RECURRENT PAROTITIS

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CLASSIFICATION OF PAROTID INFLAMMATIONS

INFLAMMATION of the parotid glands may be roughly divided into four groups (1) mumps, a specific type of infection that is contagious, (2) suppurative parotitis, an inflammatory reaction that usually occurs in the debilitated and the weak, it may follow surgical procedures, occurs during the course of the infectious diseases, and occurs in newborn infants, (3) obstructive parotitis occurs from the irritation of a calculus, and (4) recurrent parotitis, an inflammation of the parotids of obscure etiology which occurs in otherwise healthy individuals and which runs a benign course.

Little discussion is necessary on the subject of *mumps*. A rise in temperature may or may not be present and a leukopenia is usually present. It should be emphasized that before a mumps parotitis is diagnosed one should make pressure over the infected gland and milk along Stensen's duct to see whether pus exudes from the duct opening. Often no saliva can be seen. If pus is present then it can be assumed that it is not mumps that one is dealing with. Many of the cases of recurrent parotitis have been erroneously diagnosed as mumps from one to three times.

Suppurative parotitis fortunately is very rare in children. It is a very serious disease with a reported mortality of 30 to 45 per cent.¹ Surgical incision with drainage is usually necessary. As yet there have been insufficient reports on the use of sulfonamides and penicillin in these cases. Certainly they should be used and in large dosage. Suppurative parotitis of the newborn is not uncommon and apparently has a low mortality. Sanford² reported five cases treated with sulfonamides and incision for drainage in four cases with recovery in all. This type of parotitis is usually due to the *Staphylococcus aureus* although other organisms may be the infecting agent. It is felt that most infections ascend through the duct and are not blood borne. The condition is usually unilateral but it may be bilateral.

A calculus in the parotid gland or duct causing *obstructive parotitis* is extremely rare in infants and children. There is an acute onset of the swelling with usually severe to excruciating pain. Suppuration of the gland may or may not occur. Removal of the calculus results in a cure.

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Recurrent parotitis is apparently more common in infants and children than one would suppose from the few reports in the literature. During the past several years I have observed about sixty cases. Many of these had at the time of the first, second or third occurrence of the swelling been diagnosed as mumps by the family or a physician. As the infection is a rather benign one and from outward appearances is indistinguishable from mumps it is not uncommon to have a child experience more than one attack before the family seeks medical aid for an explanation. I have never seen any of the salivary glands affected except the parotids.

RECURRENT PAROTITIS CLINICAL AND LABORATORY FINDINGS

Although the average *age* at the time of the first swelling was about three to four years, cases were observed from the age of eight months to the twelfth year. The latter age level is undoubtedly due to a practice limited to pediatrics and cases observed in a clinic where the upper age of admission is the thirteenth birthday. However, four cases have also been observed in adults.

Swelling is sudden in onset as it is with mumps and it is usually the first noticeable symptom. The whole gland is involved in nearly all cases. The swelling is rarely as extreme as it often becomes in mumps and it has a nodular, firm feel with little if any edema. Although redness of the skin may occur it is not usual. The swelling may be bilateral or unilateral and recurrences may involve one side and then the other side. Usually, though, recurrences involve the same gland each time. Fluctuation is so rare that it was observed in only one patient. The maximum swelling occurs most commonly within the first forty-eight hours. Some change in size may occur during the course of the swelling. The regional lymph nodes are not enlarged. While the submaxillary glands are frequently swollen in mumps I have never seen them involved in recurrent parotitis.

Stensen's duct opening is practically always moderately red and edematous. This is in contrast to our usual observation in mumps. The expression of pus from the duct is diagnostic. The pus has a characteristic appearance. It is grayish or whitish and is flocculent with flecks and clumps of pus mixed in the saliva. We have never observed blood with the pus or saliva. This purulent material is expressed very easily from the duct opening by pressure over the affected parotid and then milking the duct along the cheek. Ordinarily one does not see the pus coming from the duct without making this pressure. Often with such pressure it will spurt from the duct opening. Usually only a small amount can be expressed at one time and further milking will not produce more for an hour or more. It seems as if there is very little pus pocketed in the duct at any one time. We have never been able to express any plug of mucus or other material which might have caused a plugging of any of the main ducts. In a

few instances purulent material was not present until twenty-four hours after the onset of the infection

In only two of the some sixty cases that we have observed have we been unable to obtain pus from the duct during a recurrence. In these cases only normal appearing saliva was obtained. In no instance was there an absence of salivary secretion from the parotid.

In mild cases the duration of the swelling may be only one to two days. In the average case it will last for two to three weeks but it is not unusual to have some swelling present for six to eight weeks or even longer. In the latter instances there will be considerable fluctuation in the size of the gland during that period. When the swelling has been present for more than two weeks the glands become more nodular and firm and resolution is slow.

The number of *recurrences* varies widely in the individual cases. In some cases we have only seen the swelling once while in others it has occurred as often as ten times. Recurrences have occurred after only a few days, after a week or a month, sometimes two or three times a year and at times after two or three years. The longer the interval between attacks the less likelihood there is of a recurrence. The severity of the swelling and the length of time it is present has no bearing upon the number of attacks or the interval between them. It has seemed to us, though, as if the younger the age of the first attack the more likelihood there is of frequent recurrences and the shorter the interval between recurrences.

Fever may or may not be present. When present the temperature varies between 100° and 104° F. Fever is usually present at the onset, at which time it is highest, and persists for only a few days. After that there may be no fever or only a very low grade one.

Pain in varying degree is nearly always present. At times it comes on a few hours before the onset of the swelling. It is rarely severe and most children do not complain of it after the first few days. The amount of tenderness varies a good deal but is rarely severe. There is rarely much objection to pressure over the gland and milking of Stensen's duct. Most often some degree of tenderness is present during the whole period that the gland is swollen.

Toxicity is rarely present even when the fever is rather high and when the involvement is bilateral. The children do not appear ill and it is difficult to keep them in bed. Most of them have little or no difficulty in eating.

In respect to the *blood count*, there is usually a leukocytosis ranging from 8000 to 18,000 present with an increase in the polymorphonuclear cells. In mild cases the blood count may be normal. As is usual of infections during infancy, the lymphocyte ratio may be high in contrast to that normally seen after the infancy period. Secondary anemia when present has no relationship to the parotitis.

X-ray examination of the parotids failed to reveal the presence of a

calculus or foreign body in any of the cases observed Sialograms, made by injecting opaque material into Stensen's duct, were obtained in a few cases and were negative

Probing of the duct was also performed in a few cases with negative results

ETIOLOGY

The etiology of recurrent parotitis is still obscure In our experience the condition has been primary in otherwise healthy infants and children There is apparently no relationship to throat infections, to the presence or absence of the tonsils or the condition of them, or to healthy or diseased gums or teeth The disease occurs just as frequently in the healthy robust child as in those with varying degrees of malnutrition There was also no relationship to a history of mumps occurring prior to the onset of the recurrent parotitis Some of the cases were observed at the time of the first swelling and mumps could be fairly safely excluded because of the presence of pus from the duct, the blood count, and the absence of mumps in other members of the family before or after contact with the patient In a few cases it seemed fairly safe to conclude that the patient had previously had mumps In two instances I have seen an apparent mumps develop in patients who had a recurrent parotitis

Pearson³ reported seventeen children with recurrent parotitis, infection of the secretion being present in six cases and no infection in eleven Sialograms revealed some dilatation of the large duct or terminal ducts in half of the cases but no point of obstruction was mentioned Sialograms were done in only a few of our cases and no evident dilatation of the ducts was observed Undoubtedly some degree of dilatation must be present to account for the increased amount of secretion above the normal that can be obtained upon pressure over the gland and duct The extent of the dilatation must be slight because of the small amount of secretion that can be obtained at any one time We have never been able to express anything that looked as if it could plug one of the main ducts

The consensus favors the theory that the infection is an ascending one from the mouth up through Stensen's duct This is borne out by the work of Berndt, Buck and Von Burton⁴ Using a hemolytic *Staphylococcus aureus* they injected Stensen's duct in ten dogs and produced a parotitis in seven of them while a parotitis developed in only three of fifteen dogs when an artery to the parotid was injected Whether infection is the primary cause of the parotitis or whether it is secondary to an already swollen parotid with salivary stasis is not known There is evidence to support the latter view Cases of recurrent parotitis occur without infection of the secretion, in other cases infected secretion is not obtained for twenty-four hours or more after the swelling occurs

Pearson³ also found a history of allergy or some allergic manifestations in eleven of the seventeen cases he reported. After a careful check of our cases we could find no relationship to any form of allergy.

In a few reported cases there seemed to be a relationship between the presence of a throat infection and the onset of the parotitis. This was not true in our series of sixty cases.

Bacteriology—Cultures of the pus from the duct opening was made in all our cases and the *Streptococcus viridans* was found in every instance. Fairly frequently *Staphylococcus aureus* and rarely pneumococcus were also found. Sanford² reported *Staphylococcus aureus* in the five cases occurring in the newborn he observed. *Staphylococcus aureus* has been reported also by others in recurrent parotitis. Why our cases were predominantly *Streptococcus viridans* infections cannot be explained.

TREATMENT

Treatment so far has been very unsatisfactory in shortening the course of the individual attacks or in preventing recurrences. All forms of the sulfonamides have been used with no apparent benefit. Penicillin has not been used but should be given a trial. We have also used potassium chlorate which is excreted through the parotid and potassium iodide without effect.

Aspirin is given for fever and for comfort. Bed rest should be insisted upon at least during the period that fever is present. Any food that is tolerated is given.

Heat or cold applied to the swelling may give some comfort but it does not influence the course of the disease.

Sedatives such as phenobarbital may be used but are rarely indicated.

We have used x-ray therapy in a number of cases with questionable results. It has seemed though, that the course of the individual attacks is shortened and that recurrences are decreased in number as the period between recurrences lengthened.

It has never been necessary to resort to surgical interference either by slitting the duct opening or incising the gland. In fact, such a procedure should be frowned upon until there is sufficient evidence that frank suppuration has occurred and other methods of therapy have failed.

It must be emphasized that recurrent parotitis is a benign condition that occurs in otherwise healthy infants and children. Surgical intervention is rarely if ever indicated. This is in contrast to suppurative parotitis, whether it occurs in the newborn or is secondary to some other infection or toxins as a complication of surgery, in which cases surgical incision is usually necessary.

No instance of contagion from recurrent parotitis has ever been observed.

REPORT OF CASES

The following short case reports are typical of the cases seen. The first one is the only case we have seen in which suppuration occurred.

CASE I—Von W., a girl born July 25, 1935, was first seen on August 10, 1939, with a history of swelling of both parotids and fever for six days. There was no preceding illness. The rectal temperature was 101.6° F and there was a marked bilateral parotitis with fluctuation (Fig 7), pus from both Stensen's ducts and a suppurative otitis media. The patient was not toxic. She was admitted to the hospital and heat was applied to both parotid areas. The day after admission both parotids began to suppurate through the skin. The leukocyte count was 24,500 with 79 per cent polymorphonuclear cells, 18 per cent lymphocytes and 3 per

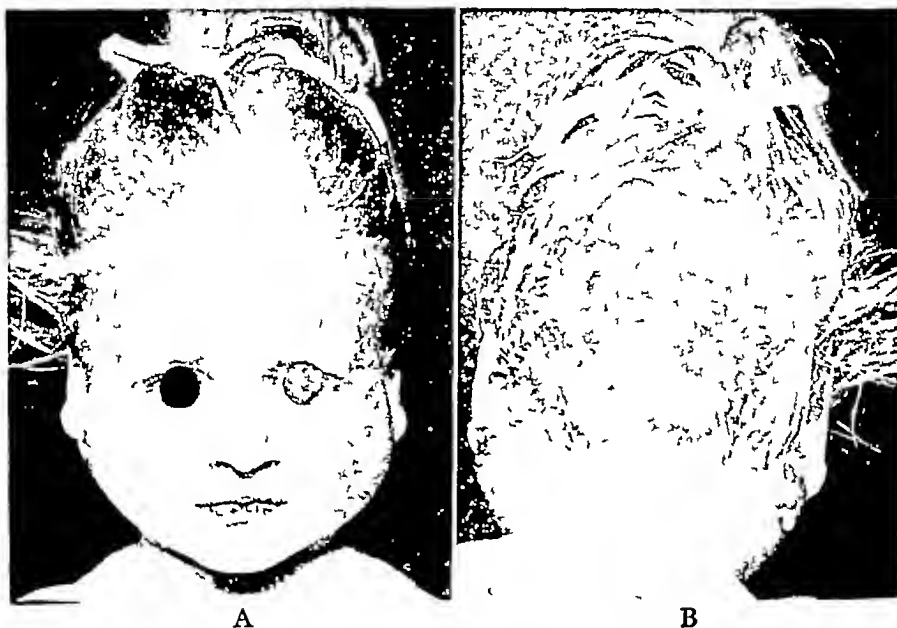


Fig 7 (Case I)—A, Acute suppurative bilateral parotitis. Spontaneous suppuration through skin seven days after onset of parotitis. Uneventful recovery. B, rear view.

cent monocytes. Examination of the urine was negative as were the serology and Mantoux tests. Cultures of the pus from the Stensen's duct opening, the parotid suppuration and the otitis media revealed *Streptococcus viridans* and *Staphylococcus aureus*. The course was an uneventful one and there was a complete recovery by September 8, 1939. There have been no recurrences.

CASE II—D. A., a girl born January 14, 1936, was seen on December 1, 1941, with a left parotitis of three weeks' duration. The swelling involved the whole left parotid and was firm, no fluctuation was present. The skin over the swelling was slightly reddened. Pus was easily expressed from Stensen's duct which upon culture showed a *Streptococcus viridans*. There had been only slight fever and when the patient was seen the temperature was 100.2° rectally. The examination was otherwise negative except for large tonsils and several carious teeth. The serology was negative and the leukocyte count was 18,900. The swelling

gradually subsided and was entirely gone by December 19. There have been no recurrences up to the present time.

The child had had chickenpox from which she recovered one week before the present parotitis. This was the third attack of parotitis. There was a bilateral parotitis in February 1941 diagnosed as mumps by another physician. In August 1941 she had a right-sided parotitis reported as mumps by still another physician.

CASE III—J A was born in February 1931 had her tonsils and adenoids removed in September 1938. There was no history of mumps. In November 1941 she was seen with a left parotitis. There was no fever. Pus was obtained from Stensen's duct and upon culture *Streptococcus viridans* was found. The swelling remained for two and one half months. She was again seen in February 1942 with

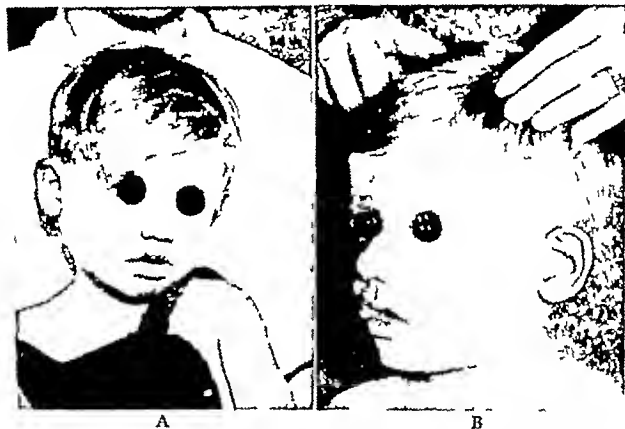


Fig 8 (Case V)—A Third recurrence of a bilateral parotitis. Although only right side is shown in this photograph the left side was similarly swollen. B, Recurrence of left parotitis only, eighteen months later.

a recurrent left-sided parotitis which lasted for one month. Cultures of pus from Stensen's duct again showed *Streptococcus viridans*. There was no fever. The leukocyte count was 8800. The examination of the urine, blood serology and the Mantoux test were negative. Roentgenograms of the parotid were also negative. There have been no further known recurrences.

CASE IV.—P P was born in August 1940. A left parotitis diagnosed as mumps by a physician occurred in April 1942. When seen in September 1942 there was a left parotid swelling which had been present for one week. Considerable fever had been present at the onset but the temperature was now normal. Pus was expressed from the duct which upon culture showed a *Streptococcus viridans*. The swelling did not completely subside until October 21, 1942, a period of five weeks from the onset. On October 1, after the parotitis had been present for two weeks, a severe throat infection with temperature up to 104° F developed. The

throat infection subsided in eight days with only a slight increase in the size of the parotitis. There have been two recurrences of the parotitis, each lasting for ten days. The first developed on November 1, 1942 and the last on May 5, 1943. In both, cultures of pus from the duct showed a *Streptococcus viridans*. Leukocyte counts ranged from 8600 to 12,350 with polymorphonuclears 34 to 43 per cent and lymphocytes 66 to 35 per cent. The tonsils were large and the mouth was clean.

CASE V—G M was born April 27, 1935. This boy was seen in January 1938 with a bilateral parotitis (Fig 8, A). *Streptococcus viridans* and *Staphylococcus aureus* grew in cultures of the pus expressed from both Stensen's ducts. There was no rise in temperature. The examination was otherwise negative as were the roentgenograms of both parotids. This was the third attack of bilateral parotitis he had experienced during the past year. Each attack lasted from one to three weeks. He was seen again in June 1939 with a left parotitis (Fig 8, B). At this time no pus could be obtained from the duct but there was mucus. The leukocyte count was 12,750 with polymorphonuclears 45 per cent, lymphocytes 44 per cent, monocytes 4 per cent and eosinophils 7 per cent. Because of these findings and the fact that there was no evident contagion it was felt that this was also a recurrence of the parotitis but without infection and not a mumps parotitis.

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BRONCHIAL OBSTRUCTION IN INFANTS AND CHILDREN

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BRONCHIAL obstruction is one of the fundamental factors in pulmonary disease. Direct changes in the lung due to a bronchial obstruction consist of emphysema or atelectasis, depending upon the degree of obstruction. Indirect, or secondary changes, as well as the serious sequelae of bronchial obstruction consist of cardiovascular changes, alterations of intrathoracic pressures which materially influence the exudation of fluid into the alveolar spaces, pulmonary supuration and damage to the bronchial walls distal to the obstruction.

The following cases are presented in detail to illustrate both the primary and secondary effects of bronchial obstruction as it occurs in infants and children. The cases are selected from those seen routinely in the bronchoscopic clinic of a children's hospital, only the significant features of each case are presented to conserve space.

CASE I COMPLETE BRONCHIAL OBSTRUCTION BY A SCREW CAUSING ATELECTASIS AND EVENTUALLY BRONCHIECTASIS

J. P. This 10 year old girl was first admitted to the hospital in December 1938. At that time she had had a persistent cough for two months. Chest pain, dyspnea and high fever developed during the last twelve days of this period, and her cough became productive of a large quantity of purulent mucopus. She appeared acutely ill but was alert and cooperative. Her face was flushed, although her lips were bluish and she was coughing continually in paroxysms and expectorating about a tablespoonful of thick, yellow material at the end of each paroxysm. Her respirations were shallow and rapid. The history prior to admission is interesting and very informative. Before this illness she had had several less acute attacks of either pneumonia or bronchitis during the past five years. These always occurred in the winter months and lasted until summer. Each winter she lost two or three months of school. She had complained of pain in her chest, especially after running or after exertion. No history of a foreign body could be elicited.

Physical examination revealed a temperature of 103.8 F., pulse 132 and respirations 36. Expansion of the chest was decreased on the left; the percussion note was dull over the left lower lobe, auscultation showed moist rales over the entire chest and bronchial breathing present over the left and right lower lobes.

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The remainder of the physical examination presented no findings significant for this discussion. The red blood cell count was 4,500,000, the hemoglobin 100 per cent, the white blood cell count 32,300, the urine was normal, blood sugar, cholesterol, chlorides and carbon dioxide combining power were normal. The Wassermann and Kahn tests were negative. The sputum examinations showed only mixed organisms. The impression at this time was that the patient had a bilateral lower lobe pneumonia with bronchiectasis or possible lung abscesses. Sputum was typed at once but showed no specificity of organisms. An x-ray of her chest showed a left lower lobe infiltration and a foreign body (a screw) in the right lower lobe bronchus, with increased bronchial markings bilaterally suggestive of bronchiectasis. The mediastinal structures were displaced slightly to the right and there were irregular densities adjacent to and behind the heart on the left suggestive of atelectasis and bronchiectasis (Fig 9).

Evidence of sepsis continued in the child for the first week following admission. The temperature, respirations and the white blood cell count fell gradually,



Fig 9—Postero-anterior and right lateral chest x-rays showing a corroded wood-screw in the right lower lobe bronchus of the first patient

and the findings in the chest changed repeatedly during the next few days. The screw was removed bronchoscopically with the aid of a biplane fluoroscope twelve days after admission. Subsequent bronchoscopic aspirations helped to reduce the amount of pus present. Five weeks following removal of the screw, a lipiodol study of the trachea and bronchi demonstrated a bilateral bronchiectasis (Fig 10). Several more bronchoscopic aspirations were done before the patient was released from the hospital three months after admission. Her general condition was satisfactory and she was followed by the bronchoscopic clinic for aspirations as necessary.

At least twice during the next five years this patient had an acute exacerbation of her pulmonary infection. Her stays in the hospital usually lasted two to three weeks. Sulfathiazole was used after her third admission with good effects. During the third hospital stay a bronchoscopic examination revealed a definite stenosis of the right lower lobe bronchus. A right lower lobectomy was recommended at this time with possibly a lobectomy of the left lower lobe at a later date. The right lower lobe was removed by Dr. Willard Van Hazel in October,

1944 and the patient made an uneventful recovery. Improvement has been satisfactory with almost complete cessation of all symptoms, and for the first time within her memory she had no respiratory infections through the winter. The lobectomy of the opposite side may not have to be done.

Many interesting aspects of bronchial obstruction become evident upon an analysis of this case. The foreign body, a flat-headed wood screw, head upward, was overlooked for many years. It represents an

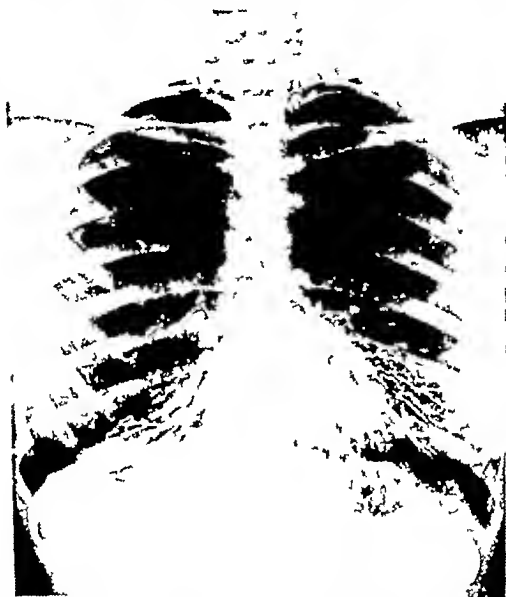


Fig. 10—Bronchogram of the same patient demonstrating extensive saccular bronchiectasis of the right lower lobe. Bronchiectasis to a lesser degree is present on the left side.

intrabronchial obstruction of a bronchus leading to a relatively large area of lung. The obstruction was complete, and consequently the air in the lung distal to it was absorbed and the collapse or atelectasis of the lung resulted. The most significant feature of this case is not necessarily the foreign body, but the fact that the bronchial obstruction it produced eventually resulted in bronchiectasis.

In adults, bronchiectasis is the commonest chronic pulmonary disease, far exceeding pulmonary tuberculosis in its incidence. In its

advanced stage the diagnosis of the disease is easily established, the history of a chronic, productive cough, occasional hemoptysis, clubbed fingers, repeated attacks of "pneumonia," physical findings of dulness and of many rales in both bases, and x-ray and bronchoscopic findings of lower lobe pulmonary suppuration are characteristic. The diagnosis is confirmed by the bronchogram which shows a saccular or cylindrical dilatation of the bronchi of a segment, lobe or entire lung. In this state of the disease the patient is a social outcast because of his foul, productive cough. This description of far-advanced bronchiectasis is too well known to require further elaboration, it is repeated here to show the end result of bronchial obstruction. In the case just shown, the bronchial obstruction which initiated the series of changes which eventually resulted in bronchiectasis was a foreign body. Any bronchial obstruction, whether it be a tumor, a bronchial compression, or an inflammatory edema of the bronchial mucosa, may initiate this same series of changes.

It is difficult or impossible to discover the nature of the actual obstructing element in each case of bronchiectasis in which a mechanical factor may be held to have a direct causal relationship. Occasionally, as in this case just presented, the obstruction is dramatically demonstrated roentgenographically when the foreign body is found at the apex of a bronchiectatic triangle. However, a far more common type of bronchial obstruction appears to be an inflammatory bronchial stenosis associated with upper respiratory infections. Such stenoses are common in childhood and manifest themselves by repeated "attacks of pneumonia" which do not follow a course typical of true pneumonia. The child becomes acutely ill, dulness, bronchial breathing, and a bronchophony are found over one lobe, usually the lower, but the heart shifts toward the involved side, demonstrating that the process is one of atelectasis rather than pneumonia. The symptoms subside as soon as the cough becomes productive of the obstructing secretions, and the temperature returns to normal within a few days. Thus, with these acute symptoms so closely simulating pneumonia, the element of bronchial obstruction may be overlooked. These cases are not uncommon, the majority recover spontaneously, or possibly after the use of expectorants. But some continue with a persistent cough and a low-grade fever. The continuation of these apparently insignificant manifestations is due to the persistence of the atelectasis, and the roentgenogram reveals a triangular density at the base of the lung. This, too, generally clears spontaneously after several weeks but has a tendency to recur, remaining present for increasingly long periods of time after each attack of "pneumonia." In a correlation of these progressive clinical and roentgenographic manifestations with the correspondingly changing endoscopic characteristics, it has been definitely demonstrated that this is actually a prebronchiectatic stage. Therefore, its clinical recognition is important. Unless successful re-aeration

of the lung is obtained, retention of pus will eventually lead to destruction of the bronchial wall and finally to bronchiectasis. As a general rule, the time interval which exists between the actual onset of such an obstruction and the eventual well-established bronchiectasis is so great that the importance of the pulmonary infections of childhood may be overlooked. Such infections occur with relative frequency in childhood, and attention must be directed toward them in any discussion of bronchiectasis.

Treatment consists in the use of expectorants, frequent adequate postural drainage and, of course, chemotherapy. Penicillin and the sulfonamides may, however be of only temporary value if adequate drainage is not obtained. If postural drainage is inadequate, endobronchial drainage should be instituted. The bronchoscopic picture of the disease during this stage demonstrates the need of active bronchial dilatation and frequent aspiration of obstructing secretions by means of a strong suction pump.

Summarizing the discussion of this first case, we may state that complete bronchial obstruction, produced in this instance by a foreign body, resulted in atelectasis and eventually in bronchiectasis. Pulmonary suppuration, hemorrhages, acute episodes of pneumonitis in the opposite lung as well as the originally diseased lung became severe complications. Eventually a lobectomy was performed to eradicate the disease. A similar clinical course follows any longstanding, complete bronchial obstruction—whether due to bronchial compression, inflammatory bronchial edema, or an endobronchial neoplasm. Early recognition of the bronchial obstruction and its prompt removal break this chain of events before bronchiectasis develops.

CASE II MEDIASTINAL PERICARDIAL AND SUBCUTANEOUS EMPHYSEMA RESULTING FROM CHECK VALVE OBSTRUCTION OF THE BRONCHUS BY A PEANUT

R. T. This 5 year old girl was recovering from measles and was given some peanuts by her parents. While eating the peanuts she choked and gagged, and although she did not become cyanotic she developed a wheeze which persisted for three days. She then developed a swelling of her shoulders, neck and face. It became worse the following day and extended down the arms to the wrists. Respirations became extremely labored, associated with occasional episodes of cyanosis.

The child entered the hospital critically ill, four days following the foreign body accident, with extensive subcutaneous emphysema and marked dyspnea. The temperature was 102° F., the pulse 132 and respirations, which were 32, were shallow and wheezing was audible. Oxygen was started immediately. Physical examination revealed crepitation over the chest, neck and arms, and wheezing was heard throughout both lung fields.

X-ray examination upon admission showed patchy shadows in the region of the right middle lobe, as are frequently seen in aspiration pneumonia. The subcutaneous emphysema extended over the cervical axillary and upper chest regions and down both arms to the elbows (Fig. 11). There was dense clouding in the region of the right middle lobe. Blood counts were normal and the urine negative. Nasal and throat cultures were negative.

A bronchoscopic examination was made two hours after admission. The larynx was somewhat edematous, and the trachea and right bronchus contained some frothy mucus. The right bronchus was obstructed by a white, irregular half of a peanut which was extracted with peanut forceps.

Improvement in breathing was immediate, and the child soon became alert and responsive. She was placed under oxygen again and within twenty-four hours her temperature, pulse and respirations had returned to normal. The subcutaneous and mediastinal air slowly absorbed and her cough disappeared. The chest



Fig. 11—Extensive subcutaneous emphysema of the neck and arms due to a partial obstruction of the right bronchus

was normal to auscultation in four days. X-ray study on the fifth postoperative day showed only a small amount of air in the cervical soft tissues, the remainder of the air had absorbed. The right lung field had cleared. She was discharged on the sixth postoperative day.

This case is similar to the first one in that the bronchial obstruction is again due to a foreign body. However, the degree of bronchial obstruction is considerably less, consequently, an obstructive emphysema rather than atelectasis is found distal to the obstruction. The mechanism of this type of obstruction is dependent upon the physiologic increase in the diameter of the bronchus on inspiration and its decrease on expiration. Thus, air passes the foreign body and enters the lung distal to the obstruction on inspiration but becomes trapped during expiration as the bronchus collapses around the foreign body. Repetition of this process many times results in marked emphysema distal to the foreign body. If the foreign body has obstructed a main

bronchus the entire lung becomes emphysematous. The emphysema persists, of course, during expiration, to give rise to the classical physical and roentgen findings of obstructive emphysema. These will be discussed later after all the cases are presented in order that comparisons can be made.

Returning to the case just presented, let us discuss more in detail the mediastinal and subcutaneous emphysema. These are interesting and serious complications of bronchial obstruction. Occasionally they are the first indication of this type of bronchial obstruction, and when found in the absence of a foreign body history a foreign body should nevertheless be suspected. The mechanism accounting for the air in the mediastinum is not entirely understood, but apparently it is the result of greatly increased pressure in the alveoli close to the visceral pleura. This causes bullae to form under the surface of the visceral pleura which may dissect along the pleural surface to reach the mediastinum under the reflections of the mediastinum which cover the primary bronchi. With further pressure the air dissects upward into the neck, spreading out from this region over the surface of the body. In extreme cases it dissects up over the face, down along the arms, and across the entire trunk and external genitalia. It usually is prevented from descending down the legs by Poupart's ligament but may cross this barrier. Pericardial emphysema is a complication in severe cases since air dissects downward as well as upward in the mediastinum. This produces cardiac tamponade and adds to the dyspnea, thus causing greater respiratory effort to further increase the emphysema. The process may take a different course if the bleb or bulla under the visceral pleura bursts before dissecting toward the mediastinum. In such an event a pneumothorax is immediately established and great intrathoracic pressure may be built up causing severe dyspnea or even a rapidly fatal pressure pneumothorax.

The management of cases of mediastinal and subcutaneous emphysema due to bronchial obstruction often requires emergency, life-saving measures. First and foremost is the removal of the bronchial obstruction. The bronchoscopy itself under such conditions is not without dangers, but must be done immediately. From this point onward, conservative measures usually suffice. These consist of mild sedatives, absolute quiet, and the immediate and long-continued use of oxygen. Oxygen not only relieves the dyspnea but is more readily absorbed from the tissues than air. In the event that these measures do not arrest the process, a cervical mediastinotomy may become necessary. If a pressure pneumothorax has developed, relief is obtained immediately by inserting a needle into the thorax or by establishing a closed pneumothorax drainage system.

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A summary of the second case shows that a partial bronchial obstruction has resulted in an obstructive emphysema which built up such a tension that a mediastinal, pericardial and subcutaneous em

physema resulted. Therapy consisted of removal of the obstruction (a peanut), oxygen and sedatives.

CASE III PARTIAL OBSTRUCTION OF A BRONCHUS BY A METAL FOREIGN BODY WITH NO SIGNS EXCEPT A WHEEZE

B C This child, also a five year old girl, was admitted to the hospital thirty-six hours after aspirating a metal reed from a toy tin whistle. Her temperature, pulse and respirations were normal. Blood counts and urinalysis were normal. X-ray examination revealed a foreign body below the bifurcation of the trachea in the right bronchus (Fig 12). It was thin, rounded and tapered below, its proximal end was sharp and straight. Physical examination was essentially negative except for a wheeze heard with the stethoscope over the right nipple. The chest showed equal expansion on the two sides and resonance was equal bilaterally, breath sounds were considered slightly louder and more harsh on the left side.



Fig 12—Postero-anterior and right lateral chest x-rays showing a metal reed in the right bronchus of the third patient. There are no changes in the lung distal to the foreign body.

A bronchoscopic examination was made shortly after the child was admitted to the hospital. The sharp, straight proximal edge was readily visualized, but its lateral borders were so fixed in the mucous membrane that it could not be extracted until a larger bronchoscope was inserted and the bronchus dilated with the lip of the tube to release the reed. Although the reed was firmly fixed in the bronchial walls, the airway was not actually occluded since air passed above and below the reed without hindrance. The child had no postoperative temperature or findings and was discharged on the second postoperative day.

The significance of this case is that it shows the manner in which a bronchus may be partially obstructed without producing changes in the lung distal to the obstruction. Consequently, physical findings are negative except for the presence of a wheeze heard during inspiration and expiration, it is loudest at a point over the foreign body. If the

A difference between the mechanics of the check-valve and the ball-valve does exist, although their ultimate action in regard to bronchial obstruction is, in most instances, identical. In the check-valve, the valve seat remains in a constant position, opening and closing as the bronchus expands and contracts. In the ball-valve, the obstructing element moves back and forth during inspiration and expiration, moving into and out of the valve seat (Fig 13). Under certain conditions, the check-valve or the similar ball-valve acts in the reverse manner,

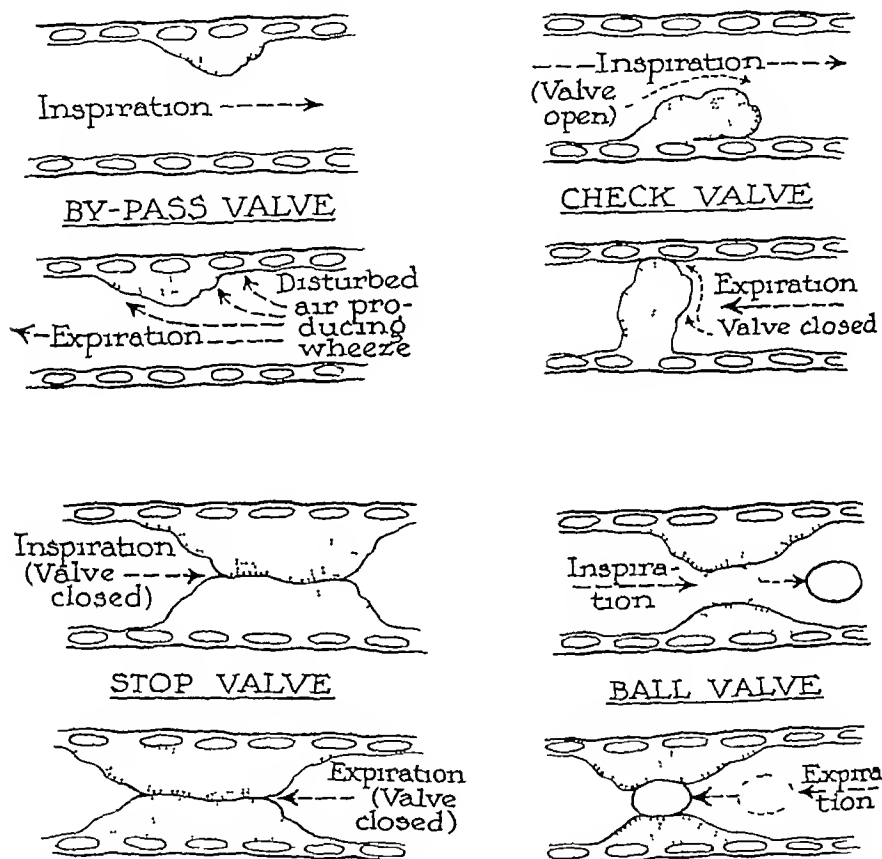


Fig 13—Diagrammatic representation of the manner in which the four types of valves act to produce bronchial obstruction

allowing air to leave but not enter a bronchus. Under such conditions, the lung rapidly becomes airless or atelectatic and the signs and symptoms are those of atelectasis.

Complete obstruction of a bronchus, allowing no air to pass the obstruction either on inspiration or expiration, is designated as a stop-valve obstruction. Following such an obstruction the air in the portion of the lung beyond is absorbed and the lung becomes airless and shrunk, or atelectatic. The opposite lung, if the atelectasis is extensive, shows some degree of compensatory emphysema. Figure 14 illus-

trates the position of the heart, diaphragm, trachea and lungs during inspiration and expiration in each of these types of bronchial obstruction.

Symptomatology—The symptomatology of bronchial obstruction is for the most part not characteristic of bronchial obstruction per se, certain underlying symptoms are fairly constant, however, influenced in each case by the underlying etiologic factor. Other symptoms become important only when they are associated with a history of a bronchopulmonary disease. A *cough*, suggestive of bronchial irritation, may not in itself be significant, but it is one of the most constant symptoms of bronchial obstruction. It may be dry and entirely un-

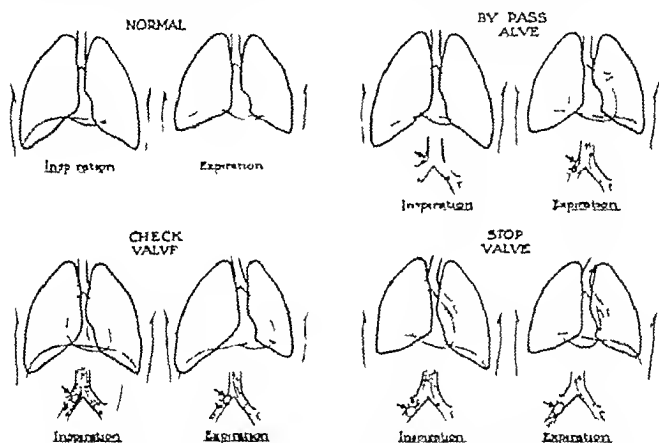


Fig. 14—Positions of the lungs, heart, trachea and diaphragm during inspiration and expiration in the various types of bronchial obstruction

productive for weeks and suddenly be associated with hemoptysis and a foul, purulent sputum produced by a superimposed infection.

The importance of the *wheeze* as a symptom of bronchial obstruction has already been stressed. With no other abnormal physical findings, the wheeze heard throughout the chest, loudest over the location of the obstruction, may be the only sign or symptom of the object if it is nonopaque to x-rays.

Dyspnea is likewise an outstanding symptom of tracheal or bronchial obstruction. All degrees of dyspnea may be noted from the rapidly fatal dyspnea accompanying an obstruction at the bifurcation of the trachea to the sensation of constriction of the chest, or "chest discomfort" which is a characteristic expression used by patients with

early bronchial neoplasms. Pain is not a common symptom unless the underlying pathological condition is extensive and associated with destructive changes. Patients with sharp foreign bodies in the bronchi rarely complain of pain, although irregular objects such as sharp bone fragments or dental fillings occasionally cause pain which the patient may localize quite accurately to the site of the foreign body.

Physical Findings—In spite of the extremely important role which roentgenology plays in the diagnosis of diseases of the chest, the physical examinations in themselves not infrequently lead to important clues which finally establish the correct diagnosis, in spite of contrasting or negative roentgen findings. One of the most constant signs in almost all cases of bronchial obstruction is a *definite limitation of motion on the involved side*, independent of the degree of the obstruction. Careful inspection of the chest is thus of great diagnostic importance in spite of its apparent simplicity. Other signs and symptoms are more dependent upon the degree of the obstruction and on its location.

Tracheal Obstruction—Tracheal obstruction may manifest itself by all the signs and symptoms of acute respiratory obstruction, leading to a rapid fatality, in the other extreme, it may manifest itself only through the simplest sign of obstruction to the airway, a wheeze. Foreign bodies loose in the trachea may be heard flying back and forth from the larynx to the carina during respiration, a finding which Jackson has designated as an "audible slap" which is accompanied by a "palpatory thud" if one palpates the larynx. The "asthmatoïd wheeze" is invariably present in such obstructions associated with a cough, dyspnea and, if the obstruction persists, cyanosis. A stridor, distinct from a wheeze, is often characteristic of tracheal obstructions, with the associated indrawing of the suprasternal notch, the epigastrium and the intercostal spaces. Tracheal obstructions due to mediastinal neoplasms not infrequently involve the esophagus as well, and consequently the child has difficulty in swallowing and regurgitates food into the trachea due to esophageal overflow.

Auscultatory findings in tracheal obstructions are a loud stridor, wheeze and sonorous rales heard throughout the chest. These are generally accompanied by a diminution of the intensity and excursion of the breath sounds and a change in the percussion note, depending upon the degree of obstruction, i. e., if an obstructive emphysema has been produced, a hyperresonant or tympanitic note will be heard, whereas if the obstruction has produced a drowned lung, the chest will be dull to flat on percussion.

Obstructions at the bifurcation of the trachea are most interesting and many times extremely confusing because they may produce opposite types of obstruction in the two major bronchi. A tumor at the bifurcation of the trachea may only partially obstruct both major bronchi, giving the findings of a bilateral obstructive emphysema. Or it may completely occlude one bronchus and partially the other, re-

sulting in an atelectasis of one lung with an obstructive emphysema of the other. A patient with this type of obstruction may present rapidly changing findings as one or the other major bronchus opens due to the extreme respiratory effort the patient makes to breathe. Two foreign bodies aspirated at the same time present findings identical to those of a tracheal obstruction. Thus, a child who chokes while eating peanuts may aspirate one part of a kernel into the right main bronchus and then, following the next cough, inspire a second piece which is sucked into the left bronchus because of the occlusion of the right. The bilateral obstruction which results is indistinguishable from a tracheal obstruction.

Obstruction of a Major Bronchus.—Partial obstruction of a major bronchus results in complete unilateral, obstructive emphysema. This is characterized by findings of limited expansion, relative hyperresonance to tympany and a marked suppression of breath sounds on the involved side. It may be accompanied by an inspiratory and expiratory wheeze and occasionally by rales or rhonchi. The heart and mediastinum are shifted to the uninvolved side on expiration and the affected side of the chest is dilated rather than shrunken. With complete obstruction to the bronchus one may have the signs and symptoms of pneumonia or an empyema due to the "drowned lung." The distinguishing feature is the marked decrease in size of the lung distal to the point of obstruction compensated by a shift of the heart toward the involved side and an elevation of the diaphragm on the involved side. There are generally many rales present, but these depend to some extent upon the degree of secondary infection. There is a limitation of motion, dulness to flatness on percussion, and frequently marked bronchial breathing and bronchophony in the early stages of the atelectasis with breath sounds entirely absent if the atelectasis is of long duration or is extensive.

Obstruction of the bronchi leading to single lobes produces varying degrees of signs and symptoms dependent, generally, upon the underlying pathological condition and degree of infection rather than upon the fact that the bronchus is obstructed. Both lower lobes are not infrequently involved in inflammatory obstruction giving relatively mild symptoms. However, the essential findings are similar to those described as following an obstruction of a major bronchus, except that they are more limited in their extent to the topographic outline of the lobe.

Roentgen Aspects.—The roentgen aspects of the diagnosis of bronchial obstruction depend upon a complete roentgenographic study of the chest. The practice of basing an interpretation on one or two views of the chest leads to gross errors not only regarding the presence or absence of an obstruction but also the location of the lesion. Fluoroscopically areas of density or emphysema, the motion of the diaphragms and the shifting position of the heart and mediastinum on

inspiration and expiration are significant. There are no actual roentgen findings in the by-pass type of valve obstruction, unless the obstructing element itself is an opaque object such as a common pin or a nail lying across the bronchial lumen. The fluoroscopic findings of the next degree of bronchial obstruction, that due to a check- or ball-valve, are of greatest importance in establishing the diagnosis. They demonstrate an increase in the transparency of the affected lung, a depression and limitation of motion of the diaphragm on the involved side, a displacement of the heart and mediastinal structures toward the uninvolved side on expiration, and finally a compensatory increase in the motion of the diaphragm on the uninvolved side. Bronchoscopic observations have confirmed the roentgen interpretation that these findings are due to the presence of bronchial obstructions innumerable times. As is well known, obstructive emphysema may be recorded on the roentgenogram by making exposures at extremes of the respiratory cycles and comparing the positions of the diaphragms and mediastinum as well as the density of the lungs on the two exposures. Thus, while a film made on deep inspiration shows both lungs completely inflated in this type of obstruction, the expiration film demonstrates the trapped air and its resulting physiologic phenomena.

The roentgen findings in complete bronchial obstruction are more obvious than those in partial obstruction because of the area of density distal to the obstruction. In complete obstructions of the main bronchi, the findings are the shift of the heart and mediastinal structures toward the involved side during both phases of respiration, the elevation and fixation of the diaphragm on the involved side, and the density of the atelectatic lung. These findings are associated with a compensatory emphysema of the opposite side. Complete obstructions of the bronchi leading to single lobes or parts of lobes have less influence on the heart and mediastinal structures although they usually do give roentgen evidence of a shift of these structures toward the involved side, thus aiding in the differentiation between an atelectasis, a pneumonic consolidation or a drowned lung. Atelectatic lobes or parts of lobes generally assume a more or less triangular shape and are frequently designated as triangular shadows. It may be generally assumed that the bronchial obstruction in such triangular shadows lies at the apex of the triangle. However, it is essential that the shadow be studied roentgenographically in two planes in order that the particular obstructed bronchus may be accurately localized.

Physiologic Effects of Tracheobronchial Obstruction—The discussion of the physiologic effects of respiratory obstruction should be amplified because their critical analysis may not infrequently result in the prevention of irreparable damage. Alterations in the intrabronchial and intrathoracic pressures directly affect the blood flow through the chest, and the secretion of fluids into the alveoli and bronchi. It has been shown that the increased positive pressure of expiration has no

appreciable effect on the blood flow. However, the increased negative pressure on inspiration has definite harmful effects which may be summarized as follows: (1) Negative intrathoracic pressure results in an increase in the pulmonary capillary blood pressure with transudation of serum into the alveolar spaces. This is a direct result of the increased negative pressure on the heart and circulation. The high negative intrathoracic pressure increases the return flow of blood to the heart so that the blood flow through the chest is increased. The flow of blood from the intrathoracic to the extrathoracic aorta and large arteries is likewise hindered by the negative pressure, thus putting an additional load on the left ventricle. As the negative pressure rises these two effects increase until a progressing accumulation of blood occurs in the lungs causing the rise in capillary blood pressure with congestion, transudation, and pulmonary edema. (2) Exudation of fluid into the alveolar spaces and bronchioles occurs because of the suction action of the intrabronchial and intraalveolar negative pressure. (3) A vicious cycle ensues, producing a further increase in the negative pressure due to the attempt to compensate for the effects of the other two actions by increasing the respiratory effort.

Thus, the physiologic effects of tracheobronchial obstruction may be divided into their respiratory and their cardiovascular actions. Mild obstruction results in a dyspnea which remains compensated by reflex and physiochemical stimulation. Severe obstruction results in respiratory decompensation, or anoxia. Long-standing obstruction results in pulmonary suppuration, bronchial destruction and bronchiectasis. The cardiovascular phenomena manifest themselves by a pulmonary edema and finally a circulatory failure due to rising intrathoracic negative pressures.

BREAST ENLARGEMENT IN PEDIATRIC PRACTICE

I P BRONSTEIN, M D., F.A.A P.,* AND EDUARDO CASSORLA, M D †

BREAST enlargement has been defined as an involvement of the mammary tissues in which these structures simulate the size, the shape, and at times the function of the adult female breast. It is our purpose to indicate and analyze in a concise fashion our experiences with the various types of breast enlargement encountered from the newborn period through puberty and adolescence. Literature on this subject has been reviewed to complement our own material.

Breast enlargement may be a matter of concern in children of both sexes, and where it persists, particularly in the male, may produce important psychological difficulties. Endocrine disturbances are often assumed in association with this phenomenon and cause additional problems in management. Hormone studies, while indicating aberrations in metabolic processes, do not as yet give exact relationships to the presenting picture; nevertheless, it is important whenever assays can be performed to collect data for future interpretation.

CLASSIFICATION

Although there is a higher incidence of breast enlargement, even a specificity, in certain age groups, involvement of the mammary tissue may occur at any age. The following grouping, which is merely a combination of our observations with those of others, emphasizes both the clinical and possible etiologic aspects. While several conditions are presented under any group in which there may be a similar microscopic structure suggesting a common etiologic factor, there may be a basic difference as to pathogenesis and prognosis modifying the individual case. It is to be emphasized that breast enlargement, unilateral or bilateral, resulting from either mammary or adipose tissue appearing as the only sign is of relatively common occurrence. Furthermore, it is frequently a part of a more intricate picture, the basis for which is often indeterminable with the present state of knowledge.

BREAST ENLARGEMENT

- I In the Newborn
- II Preadolescent Type
 - (a) Transient and persistent.
 - (b) Pseudogynecomastia

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III Associated with Obvious Endocrinopathies

- (a) Gynecomastia—hypogonadism—excessive urinary gonadotropic excretion
- (b) Sexual precocity
- (c) Addison's disease
- (d) Tumors of the testes
- (e) Thyroid affections

IV Artificially Induced

- (a) Gonadotropins
- (b) Estrogens.
- (c) Testosterone
- (d) Corticosterone

V Miscellaneous

- (a) Liver cirrhosis
- (b) Leukemia
- (c) Tumors (malignant) (very rare)
- (d) Massive involvement in girls
- (e) Associated with atrophy of the testicle following orchitis and trauma

BREAST ENLARGEMENT IN THE NEWBORN

A high percentage of newborn infants show some breast swelling by the fifth or sixth day. About two thirds of these secrete a colostrum-like fluid usually followed by small amounts of milk. Instances of secretion persisting up to twelve months have been reported. There may be a correlation between the duration of secretion and the birth weight.

These breasts are histologically miniature lactating glands attaining their development through the influence of estrogenic and mammotropic hormones derived by placental transmission. These factors have been assayed for in the urine of newborn babies.

The enlargement disappears spontaneously within a variable period. *Treatment should not be attempted* as infection resulting from expressing the secretion may lead to abscess formation and, occasionally to permanent damage of the gland.

PREADOLESCENT BREAST ENLARGEMENT

Transient and Persistent Types.—The transient and persistent varieties are described together since their clinical peculiarities are similar. They occur in boys (Fig 15, *A* and *B*) usually between the years of 13 and 18 and in girls between the ages of 8 and 12 years. Jung and Shafton, upon the basis of approximately 1000 period examinations in boys and men, were of the opinion that the occurrence of preadolescent enlargement is an integral part of the process of puberty.

The swelling, either unilateral or bilateral, varying in size from 2 to 5 cm. in diameter, forms a roughly spherical tumor directly behind the nipple. Where the swelling is unilateral it may be followed by engorgement of the other side within a variable period even as long as a year or more. Whereas the areola may become pigmented and the nipple flattened and retracted, this has not been commonly encoun-

tered in our experience. Histologic examination reveals an increased physiologic hypertrophy of the pericanalicular and periacinous tissues similar to that observed after estrogenic administration.

Trauma, allergy and hormonal imbalance have been among the hypotheses advanced to explain this condition, but none have been substantiated. With regard to hormonal factors the ratio of estrogens to the 17-ketosteroids rather than the individual rates of excretion of either of these may play an important part.

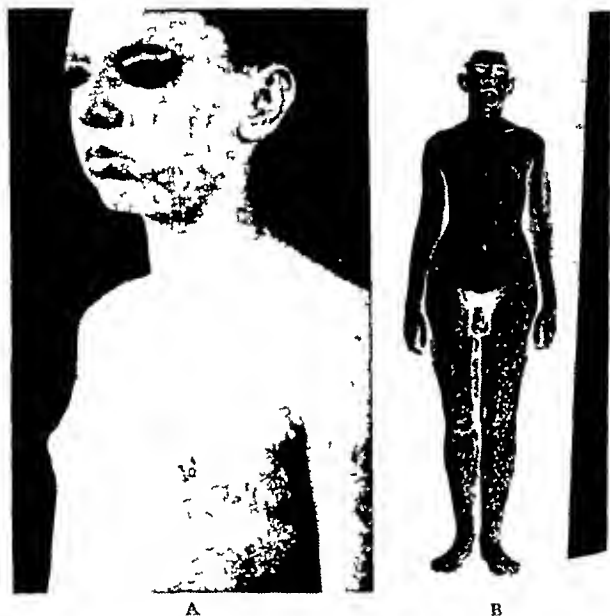


Fig 15—A B, Preadolescent breast enlargement.

The course is not predictable. Some of the swellings disappear completely within a few weeks, others last for years. In the persistent cases of breast enlargement in males traced back to adolescence in which operation was done in young adulthood, the microscopic picture is similar to that found in chronic cystic mastitis in the female. No instance of malignancy is reported in the patients with long-standing preadolescent breast enlargement. However, the importance of the psychological aspect is worthy of emphasis. It is our experience that

most of these breast enlargements involute spontaneously within a few months. Surgical intervention may be advisable if there is no tendency to involution and especially if personality changes become prominent. Since the war our indication for surgical interferences has been modified. Hormonal therapy with androgenic substances is not indicated where sexual development is adequate.

Pseudogynecomastia—Breast enlargement in this condition occurring in both girls and boys (Fig. 16) is a part of the general picture of the



Fig. 16—Pseudogynecomastia.

obesity involving also the girdle and suprapubic areas. The involvement is bilateral, is unassociated with discomfort, and tends to assume the size and shape of the adult female breast. Gland tissue is not ascertainable, the swelling being apparently formed by adipose tissue.

Obesity in childhood being the most common so-called endocrinopathy encountered in pediatric practice makes this condition important from the point of view of incidence. Confusion of this condition with Frohlich's syndrome or dystrophia adiposogenitalis is not uncommon.

mon. From our studies of these children we have come to the conclusion that neither pituitary nor thyroid disease need be postulated. We recognize the possibility of a temporary aberration in the endocrine system or in the hypothalamus which may spontaneously correct itself at puberty except in those children who are mentally

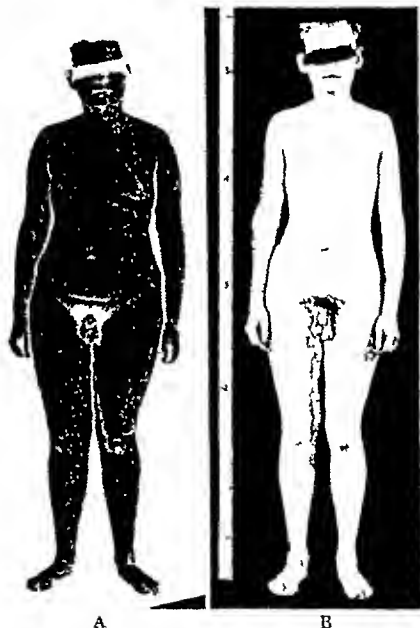


Fig 17—A, Pseudogynecomastia in a young boy B, After general weight reduction.

retarded. In the therapy of obese children endocrine treatment did not cause any alteration in the redistribution of fat. With the general loss of weight the breast condition is also rectified (Fig 17, A and B).

BREAST ENLARGEMENT ASSOCIATED WITH OBVIOUS ENDOCRINOPATHIES

Gynecomastia with Small Testes, Aspermatogenesis and Excessive Urinary Gonadotropins.—In February, 1939, one of us described a male patient, aged 17 years, with bilateral gynecomastia. The boy's breasts were neither painful nor inflamed and secreted no milk. Our patient had pubic and axillary hair but none on the face or chest. The penis

and scrotum were normal, both testes were definitely undersized, containing no irregularity or tumor masses. Seminal emissions, erections and spermatozoa were absent. Assays of the urine for estrogenic hormones were negative. Of particular interest was the finding of a positive Friedman test (Reaction III) indicating excessive quantities of urinary gonadotropic hormones.

In children, little if any urinary gonadotropic substance is found, in young adults from 4 to 19 mouse units have been assayed. The exact interpretation of this excess of urinary gonadotropin is conjectural, whether it signifies pituitary dysfunction leading to abnormal mammary hyperplasia or is the result of the deficient testicular development is problematical.

Klinefelter and co-workers described a similar syndrome, beginning during adolescence, with hypogonadism involving chiefly the tubular tissue, bilateral gynecomastia, small testes, aspermatogenesis, increased secretion of follicle-stimulating hormone with a reduction usually in the 17-ketosteroids. Microscopic study of the breast tissue showed ductal hyperplasia with proliferation of the periductal connective tissue, testicular biopsy revealed hyalinization of the seminiferous tubules with the interstitial cells being normal. Androgenic, estrogenic and corpus luteum therapy were of little value.

We have had some experience with boys exhibiting gynecomastia and hypogonadism in whom testosterone therapy was partially efficacious. We studied a boy (Fig 18), aged 17 years, in whom a diagnosis of bilateral abdominal cryptorchidism was made, there was an associated breast enlargement. Prior to our seeing him he received 35,000 R U of chorionic gonadotropins without any change. After several hundred milligrams of testosterone were administered parenterally he grew some facial hair and there was an increase in the size of the genital structures. Abdominal exploration revealed atrophied non-functioning testes. Following the bilateral orchidopexy another 10,000 R U of chorionic gonadotropins were given with no results. Further therapy with testosterone improved the general condition, maintained partial male sex function and the breast enlargement decreased somewhat.

Sexual Precocity—Breast enlargement may be one of the striking symptoms of sexual precocity. While it is not within the scope of this paper to discuss the etiology and pathogenesis of this entity, an enumeration of some of these conditions is warranted.

Hypothalamic Lesions—Sexual precocity may be associated with hypothalamic lesions without gross changes in the known endocrine glands and without recognizable evidence of intracranial disease. It is the opinion of some that this is the only type which is responsible for true precocity of sexual development. We studied the case of a 22 month old girl (Fig 19) with manifest precocious sexuality in whom necropsy revealed what was interpreted as an ectopia of

brain tissue between the infundibulum and the mammary gland. The breasts were enlarged, the mother reported that they had been growing presumably since birth. Microscopic study of mammary tissue revealed a stroma composed of wavy, collagenous fibers well embedded in which were numerous glands. There was marked hyperplasia of the epithelium of the glands, some of which showed pronounced cystic dilatation with an amorphous content of cellular



hypophyseal apparatus plays a part in the production of the picture. We have encountered occasional instances in girls aged 3 to 5 years in which the breast enlargement was the only evidence of sexual advancement. Spontaneous disappearance of these swellings occurred within a year. In an experience with one 2 year old female child, in addition to the breast swelling vaginal bleeding appeared on two occasions. This was accompanied by increased levels of estrogens as revealed by urinary assay. The process involuted within a few months.



Fig 19—Sexual precocity in a 22 month old girl

In one 15 month old girl mammary enlargement was the only symptom. Thorough study, including vaginal smears for epithelial types, revealed little. The process cleared spontaneously.

Osteodystrophia Fibrosa Disseminata (Albright's Syndrome)—This rare bizarre syndrome of sexual precocity has been reported in female children in association with disease of the bones, characterized by lessened osteoclastic resorption, fibrosis of the marrow spaces, cyst formation, and melanotic pigmentation. Hyperparathyroidism is not

clearly present. Exophthalmic goiter has occurred in some of the recorded cases

Ovarian Lesions—Granulosa cell tumors and teratomas of the ovary are associated with breast enlargement and generalized feminization. Urinary hormone assays have shown increased excretion of estrogens whereas the levels of the other hormones remain normal. These tumors

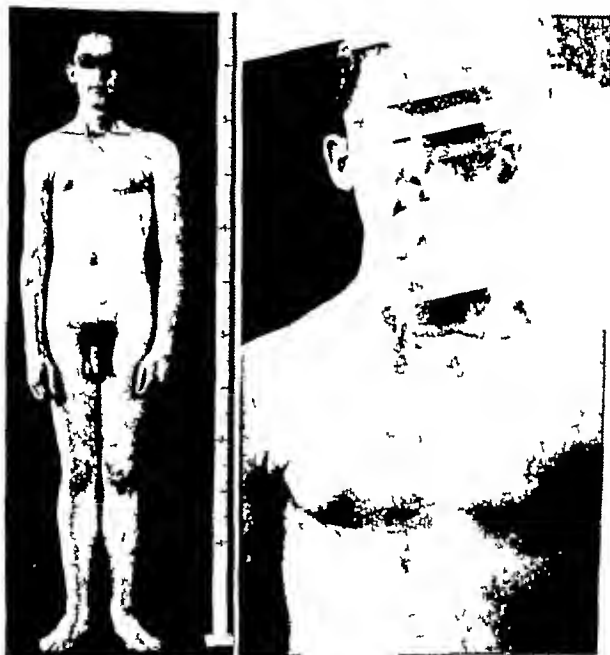


Fig 20—Bilateral gynecomastia in a 14 year old boy with history of aberrant thyroid

have been reported in girls as early as under one year. Removal has led to restitution.

Adrenal Cortical Tumors and Hyperplasia—These produce, as a rule, signs of masculinization. However, there are several cases reported in the literature in which there have been symptoms of feminization. This latter condition is extremely rare in childhood. Studies have revealed an increase in the level of

in the urine. As the adrenal cortex is probably a source of estrogens, mammary development might be explained on this basis.

Breast Enlargement Associated with Addison's Disease—Cases of breast enlargement occurring during the course of Addison's disease have been reported in the literature. This is rare in children. The mechanism is a matter of conjecture. In one case followed throughout life the breast enlargement persisted until death. Autopsy revealed hyperplasia of the breast tissues.

Breast Enlargement Associated with Tumors of the Testis (rare in children)—Gilbert analyzed 135 cases of breast hypertrophy associated with malignant testicular tumors, particularly chorioepithelioma. He found that breast enlargement, usually bilateral, was often the only clinical symptom present. The areola appeared darker and sometimes enlarged, secretion was also detectable. Pathologically, hyperplasia of the glandular tissue and pituitary changes as seen in pregnancy were found in addition to the testicular tumor.

Breast enlargement may also be associated with interstitial cell tumors. The mechanism responsible for the changes in the breast is not clear.

Breast Enlargement Accompanying Thyroid Affections—The mammary gland may show early hypertrophy in either sex when hyperthyroidism is present. Basedow reported a case of a male patient with hyperthyroidism along with swollen breasts secreting colostrum. As far as we know, no hormone assays have been made. There is some experimental evidence pointing to the increased rate of metabolism as directly responsible for the breast changes.

We recently studied a 14 year old boy (Fig 20, *A* and *B*) (August 1944) who was referred chiefly because of bilateral gynecomastia. He was adequately developed physically (sexual) and mentally. He had a history of multiple excisions for an aberrant thyroid since the age of 5 years. Endocrinological studies failed to reveal any positive findings. Urinary hormone assays were not performed. There was no evidence of dysfunction of the thyroid, either hyper- or hypothyroidism. The presence of the bilateral aberrant thyroid with the history of recurrences led to a bilateral total thyroidectomy. The microscopic diagnosis was a papillary adenocarcinoma of the thyroid gland. No changes have been noticed in the breasts since the operation (three and one-half months).

BREAST ENLARGEMENT RESULTING FROM ADMINISTRATION OF HORMONES

Gonadotropins—Chorionic gonadotropins have produced breast swellings on numerous occasions when the material was administered either for unilateral or bilateral cryptorchidism. The doses administered in these conditions are not very great (3500 to 7000 R U) and the breast enlargement, which is usually slight, disappears upon stopping this drug. In a boy with a so-called "Frohlich's syndrome" the

administration of 100,000 R.U. of gonadotropic material produced mammary enlargement which disappeared spontaneously with the cessation of therapy. Interestingly it failed to affect a presumable bilateral abdominal cryptorchidism as well as a redistribution of fat—in fact, the child gained considerable weight during the period of administration of this hormonal substance.

Estrogens.—In an early experience utilizing the mechanism of antagonism of hormones we administered 100,000 units of naturally occurring estrogenic substances to a boy with hypergenitalism. We were able to affect his condition favorably noticing as one of the results bilateral breast enlargement. Preadolescent girls with gonorrheal vaginitis treated with stilbestrol have developed breast enlargement which disappears with cessation of therapy. Oral stilbestrol therapy has been employed in male hypersexualism, and gynecomastia has appeared after the use of 375 mg. Dunn has pointed out that the physical characteristics of the breast tissue reaction to stilbestrol and the naturally occurring estrogenic substances are dissimilar. Stilbestrol-induced mammary tissue growth is firmer and the rate of resolution is slower after therapy is discontinued.

Testosterone—Gynecomastia has been observed following the use of oral methyltestosterone. It may appear as early as thirty days after the initial dose and occurs as a tender nodule, 3 to 4 cm. in diameter, placed behind the areolae. Secretion is usually not present.

Corticosterone—Gynecomastia has been observed in Addison's disease after therapy with corticosterone.

MISCELLANEOUS CONDITIONS

In the interest of completeness mention is made of the following miscellaneous conditions which may give rise to breast enlargement. Our experiences with them have been sporadic and limited.

Cirrhosis of the liver conceivably may lead to breast enlargement. A case has been reported which at necropsy showed testicular, pituitary and thyroid lesions.

Leukemia has been reported as associated with breast enlargement.

Carcinoma of the breast, a total of 4628 cases, was studied by Harrington. Two instances only were recorded in patients between the ages of 17 and 19 years.

Enlargement (mastitis gargantuan) has been reported in a girl of 14 years. The swelling was painless and began eight months prior to the onset of the menses which occurred at 13 years of age. The patient was operated upon; the left breast weighed 71 kg, the right 118 kg. On section the gland, acini and lobules showed marked hyperplasia in addition to large amounts of fibrous tissue.

Breast enlargement in association with *testicular atrophy* following orchitis and trauma has been observed; the responsible mechanism is not clear.

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ACUTE HEMATOGENOUS OSTEOMYELITIS IN INFANCY

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THE subject of acute pyogenic bone infection has been an important one because of the seriousness of such disease. In former years the death rate in these cases has always been high, and of those patients who recovered, a considerable percentage were left with a chronic bone involvement which required repeated surgical therapy, and often recurring discharging fistulas were the source of considerable morbidity. In the young age group this disease is particularly prevalent.

Originally acute osteomyelitis was considered essentially a surgical disease, the concept of early and free incision and evacuation of pus having been applied here as well as to other forms of pyogenic infection. In the last fifteen years or so, even before the advent of the revolutionary methods of chemotherapy, a school of thought has been making itself felt, which advocated the conservative handling of acute osteomyelitis, withholding any surgery during the first few days of the illness, limiting the procedures done in the acute stage to the incision and drainage of soft tissue abscesses, and limiting handling of the bone to mere evacuation of subperiosteal abscesses. With the advent of the sulfonamide drugs the management of acute osteomyelitis has swung further to the conservative side. The adherents of a hands-off policy have increased in numbers with newer methods of chemotherapy and some observers are in favor of complete non-intervention even when obvious accumulations of pus have appeared in the soft tissues. Thus acute osteomyelitis has gradually developed into a condition the management of which is essentially medical. In view of this fact, the pediatrician should be prepared to assume the full responsibility for the care of acute osteomyelitis, the surgeon and the orthopedic surgeon being assigned the role of consultants for the handling of special aspects of the problem, such as evacuation of abscesses, immobilization, and the treatment of chronic osteomyelitis including sequestrectomy.

In infancy, osteomyelitis appears to have certain characteristics which are different than those seen in the older child and adult. Green¹ pointed out that the specific etiologic factor in this age group is more commonly the streptococcus (63 per cent), whereas in older children the Staphylococcus aureus is the commoner cause (91 per cent). He found the mortality rate in his series of cases of ninety-five infants

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to be 21 per cent, other observers have reported a higher mortality (40 to 60 per cent) Under six months of age in Green and Shannon's² series the mortality was 44 per cent In those cases in which survival occurred, healing was more rapid, sequestration and recurrences infrequent, and complete eventual resolution of the lesion in the bone the rule Green and Shannon attributed the character of the local bone reaction in this age group to structural and physiological differences In infants as well as in older children, osteomyelitis has its origin in the metaphysis Once the infection is under way it follows the path of least resistance In infants there is a minimal amount of cortical bone at the metaphysis, so that spread to the subperiosteal space is direct The periosteum, more loosely attached at this age, is dissected from the cortical bone and the resultant subperiosteal abscess may rupture into the soft tissues without necrosis of the shaft In contradistinction in the older child the usual picture of a chronic bone disease with sequestration, sinus formation and frequent recurrences is the rule

With this distinction in mind it is readily appreciated that in infancy acute osteomyelitis is essentially a septicemia with localization in the bone, and that in its management the blood stream infection and the primary portal of entry merit prime consideration Here again, therefore, the therapy resolves itself essentially into medical management From Green and Shannon's mortality figures we note that the young age group, under six months, has the poorest prognosis In the newborn, acute osteomyelitis may also occur, usually as a manifestation of sepsis Stone³ states that osteomyelitis in the newborn appears to be a benign disease, but when it is a manifestation of sepsis the prognosis is graver, and depends upon the severity of the septic process Here, again, a distinction must be made relative to the prognosis of the local bone lesion in contradistinction to that of the general disease If the infant survives the septicemia, the bone lesion will usually go on to complete eventual resolution, and in that sense osteomyelitis is benign, as Stone states Septicemia, however, in the newly born is not a benign disease and the attention of the pediatrician should be focused on its therapy

CASE REPORTS

I wish to present a series of ten cases of acute osteomyelitis in infants under two years of age observed at Cook County Hospital, Children's Division These infants were all treated with sulfonamide drugs or penicillin and all recovered One, the most severely ill, was a newborn infant and since this baby presented several striking features I desire to present her case in detail Three other cases will be described somewhat more briefly and the balance presented in tabular form

CASE I—M M., a white girl 2 weeks of age on June 18, 1943, was admitted to the infant ward of Cook County Hospital from the Chicago Foundling Home, because her temperature had been elevated since birth. On admission there were no outstanding physical findings, but in view of the fever a spinal puncture was done. Meningitis of the newborn may occur without any physical signs of such involvement. In this instance the fluid was water clear, Pandy negative, and the cell count 34 lymphocytes. On culture no bacterial growth was obtained. In a few days a left purulent aural discharge developed. The pus on culture yielded staphylococci. The initial blood culture drawn the same day yielded *Staphylococcus aureus*. From the date of admission until the patient's discharge from the hospital about a year later this organism was cultured with ease from her blood and from all other exudates studied.

The child continued to have fever and several days after the appearance of the aural discharge a right parotid swelling developed which rapidly went on to suppuration. The resultant parotid abscess was first aspirated then incised and drained, yielding the same hemolytic *Staphylococcus aureus*. At about the time the parotid abscess was developing about one week after admission, a swelling of the left index finger appeared. This also rapidly softened, was incised and drained, and on culture yielded hemolytic staphylococci. X ray revealed a destructive process in the first phalanx of the left index finger. At about this time, two weeks after admission a chest film was taken which revealed a marked destructive process in the left scapula as well as osteomyelitis of the right fifth rib. The child was desperately ill during this period. Shortly after these three areas of osteomyelitis were discovered soft tissue abscesses developed in the left axilla, over the left scapular area, and in the region of the left nipple. All of these were incised and drained as fluctuations appeared, staphylococci being cultured from the pus in each instance.

Therapy in this severe case of *Staphylococcus aureus* hemolyticus septicemia of the newborn was with sulfonamide drugs in addition to the usual supportive measures such as parenteral fluid and blood and the injection of staphylococcus antitoxin. On admission on June 18 the child was placed on sulfadiazole orally. This was continued to July 8 a total of 27.5 gm being administered. From July 8 to July 24 sulfadiazine was administered in large doses, a total dosage of 22.7 gm. being given. From July 24 to August 14 sulfathiazole was administered in a total dosage of 31.5 gm. then from August 14 to December 1 sulfadiazine was again administered a total dose of 30.4 gm. being given in this period. The total dose of the sulfonamide was, therefore, 38.7 gm of which 32.67 gm. was sulfadiazine and 5.9 gm sulfathiazole. On this therapy the child gradually improved, becoming afebrile in about six weeks and remaining so thereafter. The lesion in the scapula gradually began to recalcify as did the osteomyelitis of the rib and the phalanx. A discharging sinus persisted over the left scapular area but the other soft tissue abscesses healed in a relatively short time.

The child began to grow and gain after termination of the febrile period, and she looked and acted well. In spite of these facts, however organisms could be cultured from the blood with ease up to the time of her discharge February 21 1944. She was readmitted one week later and remained in the ward until July 21 1944. During this period she continued to have a draining sinus over the left scapula. On x ray a chronic osteomyelitis with sequestration was noted in the left scapula and a chronic osteomyelitis was still present in the right fifth rib. The child was afebrile except for an intercurrent bronchopneumonia and laryngotracheitis in April and gained and developed in a normal manner. Thirteen blood cultures were drawn during this period four of which yielded hemolytic *Staphylococcus aureus*. The last positive culture was obtained May 9 1944. During this period no sulfonamides were administered except in the therapy of the intercurrent acute respiratory episode. No surgery of any sort was undertaken during

this period The infant was discharged in good condition, but with a chronic osteomyelitis and draining sinus on July 27, 1944 She has continued under observation for this condition The scapula has undergone remarkable reossification

This infant presents an illustration of an osteomyelitis in a septicemia of the newborn, the invading organism having been a hemolytic *Staphylococcus aureus* The portal of entry was undoubtedly the upper respiratory tract, a suppurative otitis media and parotitis occurring as initial complications The osteomyelitis was multiple and in no sense could the infection here be considered benign The child was given large doses of sulfathiazol and sulfadiazine over a long period of time In spite of the continued use of the drug, organisms were cultured with ease from the blood stream for many months The total dosage of the drug was enormous, but no detrimental effects were observed Multiple intravenous blood transfusions and large doses of vitamins were administered throughout the infant's hospital stay *Staphylococcus antitoxin* was used but no apparent effect could be noted from its administration

In contradistinction to this severe form of septicemia with bone localization I should like to present another young infant as an illustration of the paucity of symptomatology that may be encountered in this age group.

CASE II—E N, a Negro female infant 7 weeks of age, was admitted to the infant ward with a history of a swelling having been noted on the chest wall for about one week The infant was otherwise healthy in every respect. There was no fever Examination revealed a nonfluctuant swelling on the right lower chest wall On x-ray an enlargement of the anterior portion of the right sixth rib was noted with a destructive process in the bone. No surgery was carried out and no chemotherapy was instituted The infant remained under observation in the ward for three weeks and was discharged in good condition Shortly before discharge a second x-ray revealed some recalcification in the involved area

This young baby must have had a septicemia in the newborn period with localization in the rib In this case, however, the symptom complex was certainly benign, requiring no therapy, the type of disease Stone had reference to

CASE III—K P, a white girl 3 months of age, also was seen with isolated osteomyelitis of the rib, and since she was the only infant in which bone surgery was done, I should like to present her case briefly This child was also brought in because a swelling had appeared on the right chest wall The infant was afebrile and was doing well otherwise An x-ray taken on admission was interpreted as an osteochondroma of the seventh rib by the roentgenologist and for this reason the resident called the surgical department in consultation The lesion was explored and on incision thick creamy pus was evacuated which yielded *Staphylococcus albus* on culture The rib was perforated and found to be the seat of an osteomyelitis No bone instruments were used The child was first given sulfathiazole in total dosage of 12 gm and then sulfadiazine 10.5 gm., a total dose of

77.5 gm. of sulfonamides. Blood culture after surgery revealed *Staphylococcus albus* and was sterile just before discharge. The patient remained in the hospital for about one month and was discharged in good condition.

It is my feeling that this infant would have been better managed without any surgical intervention, as in Case II.

Penicillin gives indication of being even more effective than the sulfonamides in the management of osteomyelitis in infancy. Furthermore, it has the added advantage of being less toxic. While we have had little difficulty with the sulfonamides, we must always be wary of side effects, and must watch urinary excretion most particularly. In the case of penicillin, this necessity is virtually eliminated.

CASE IV.—H. C., a Negro girl 22 months of age, was admitted March 31, 1945 with a history of injury to the right leg. She was febrile and on examination revealed a swelling of the entire right lower extremity with inability to use the leg and pain on passive motion. Immediate blood culture yielded hemolytic *Staphylococcus albus* and on x ray an osteomyelitis of the proximal end of the right tibia with diffuse periosteal elevation over the entire bone was found. The child was given 30,000 units of penicillin every three hours intravenously until a total dosage of 4,200,000 units was administered. A soft tissue abscess developed which was incised, penicillin being injected locally into the abscess cavity. Pus from the abscess yielded hemolytic *Staphylococcus albus*. The infant improved rapidly and was discharged April 28, 1945 in good condition. Bone changes were still present on x ray examination but the incision was entirely healed and dry. Blood cultures on April 3 and April 13, 1945 were sterile.

This case is a good illustration of the point made by Green and Shannon. An osteomyelitis developed as a result of a *Staphylococcus albus* septicemia, the organism lodging in the nutrient vessel of the upper tibial metaphysis. The cortical bone was quickly perforated and an extensive subperiosteal abscess developed which quickly perforated into the soft tissues. The resultant soft tissue abscess was evacuated and under local and systematic penicillin therapy the septicemia cleared up and the local disease rapidly improved. The osteomyelitis undoubtedly will undergo complete resolution.

In the accompanying table a résumé of the entire ten cases is presented. It will be noted that none of these infants died, and that in only one case, that of the newborn reported in detail, was a resultant chronic osteomyelitis observed, though several of the infants have not been followed long enough to be sure that resolution of the bone lesion will be complete. On the basis of past experience, however, we may be almost certain that such will be the case.

This small series differs in some respects from the usual experience in osteomyelitis in young children. Eight of these infants were black, while most reported series reveal a predominance among the whites. Five were white and four Negro, probably a reflection of the admissions to this hospital.

RESUME OF TEN CONSECUTIVE CASES OF ACUTE HEMATOGENOUS OSTEOMYELITIS IN INFANTS

Case	Age	Sex	Race	Admitted	Discharge	Primary Illness	Bones Involved	Culture	Cbemothrapy
I M M	2 wk	F	W	6/17/43 2/28/43	2/21/44 7/27/44	Otitis media Parotitis	Left index finger Left scapula Right fifth rib	Spinal fluid—0 Blood —Hem staph aureus Parotid — “ “ Scapula — “ “ Breast — “ “	Sulfathiazole, 59 gm. Sulfadiazine, 326 7 gm. Total, 385 7 gm
II E L	7 wk	F	N	4/26/41	5/14/41	None	6th right rib	None	None
III K. P	3 mo	F	W	12/ 5/43	1/ 4/44	None	7th left rib	Blood—staph albus Rib — “	Sulfathiazole, 12 gm. Sulfadiazine, 10.5 gm Total, 22 5 gm.
IV S H	4 mo	F	N	4/ 2/45	6/11/45	Infectious diarrhea	Right femur	Blood—staph albus	Sulfathiazole 7 5 Gm Penicillin, 1,300 000 U
V J K	7 mo	F	W	3/ 4/41	4/ 1/41	Pneumonia Empyema	Left humerus	Blood—0	Sulfathiazole, 6 gm.
VI R H	9 mo	M	N	5/7 /45	6/ 8/45	Right pneumonia	Head right humerus	Blood—staph albus	Sulfathiazole 21 gm Penicillin, 560,000 U
VII N H	11 mo	F	W	7/29/41	9/ 7/41	Pneumonia Empyema	Left second rib	Blood—staph aureus	Sulfathiazole, 108 5 gm.
VIII J B	11 mo	M	W	11/20/41	12/22/41	Cervical adenitis	Left humerus	Blood—0	Sulfanilamide, 15 gm Sulfathiazole, 18 gm.
IX M F	18 mo	F	W	1/ 2/42	2/ 1/42	Upper respiratory tract infection	Right tibia	Blood—Hay bacillus (con taminant)	Sulfathiazole, 19 gm.
X. K C.	22 mo	F	N	3/31/45	4/28/45	Injury, right leg	Right tibia	Blood —staph albus Abscess—Hemolytic staph. albus	Penicillin 4,200,000 U Local penicillin

The primary illness differed widely. Five of the ten infants had some sort of involvement of the respiratory tract prior to the onset of the osteomyelitis. In one chickenpox, with a resultant boil on the left shoulder, preceded an osteomyelitis of the left humerus. In one severe diarrhea preceded the bone involvement and in one an injury to the leg preceded it. In the remaining two both young babies, one seven weeks and one three months of age, a swelling of the chest wall appeared as the first evidence of osteomyelitis of a rib in previously healthy infants.

Organisms were recovered from the blood in six cases while in four blood cultures were negative. Of the six a *Staphylococcus albus* was isolated in four instances, and in two of these the same organisms were recovered from the soft tissue or subperiosteal abscesses evacuated. In the remaining two cases *Staphylococcus aureus* was obtained and in one of these the same organism was consistently grown from the many soft tissue abscesses which appeared. From one child in whom a staphylococcus was isolated on two occasions a pneumococcus was recovered in one culture, but since the child developed an intercurrent pneumonia at this period while in the ward, this must be considered evidence of a cross infection. This finding while consistent with the general statistics in cases of osteomyelitis in childhood, is in contrast to the findings of Green and Shannon, who state that the streptococcus is more commonly found in infants.

The bone in which localization occurred in this series was the right tibia in two cases, a rib in three instances, the left humerus in two and the right humeral head in one, the left scapula, right fifth rib and first phalanx of left index finger in one, and the proximal end of the right femur in one. Single bone involvement occurred in all but the one newborn infant with multiple bone involvement whose case is reported in detail. This child is definitely left with a chronic osteomyelitis. The infant with the destroyed right humeral head will probably have continued disability. The remaining eight infants will in all probability go on to complete restitution of the involved areas.

Three of these infants were treated with penicillin, the remaining seven with sulfonamide compounds. The dosage is noted in the table. The effectiveness of this therapy is essentially in combating the septicemia. The local effect of the sulfonamides in the bone lesions is open to much skepticism. If the concept of the pathogenesis of these cases is correct, namely, the development of a thrombophlebitis of a nutrient vessel and the subsequent occurrence of an area of infarction in the metaphysis, the ability to transport the drug to the local area of involvement is probably lost. In addition, the ineffectiveness of local sulfonamide in pus-containing lesions is also well known. Whether or not penicillin is more active in the local area of infection still requires clarification. It undoubtedly is an extremely effective drug in septicemia usually encountered in these cases of osteomyelitis.

COMMENT

Symptomatology—From the above examples it will be appreciated that the symptoms of acute hematogenous osteomyelitis in early infancy are very variable. In the newborn period several distinct syndromes may be seen associated with suppurative bone involvement. An acute hematogenous osteomyelitis may occur which is a manifestation of a sepsis. This is the type of case we are discussing. Another syndrome may occur in the newborn which is characterized by an osteomyelitis of the maxilla. These infants are not included in this discussion since such cases probably occur as a result of direct extension from local infection in the sinuses (Poncher and Blayney),⁴ in a tooth bud, or according to Wilensky⁵ by way of the blood stream as a result of a thrombophlebitis of a nutrient vessel.

In the Newborn—In acute hematogenous osteomyelitis in the newborn two distinct syndromes may be recognized. A *benign form* occurs in which the infant presents himself with an osteomyelitis involving one of the long bones usually with little or no complaint other than the local disability. These infants usually give no history of preceding illness, their growth and development have been progressing normally, but a local area of swelling and dysfunction is noted by the parents over one of the long bones. On x-ray an osteomyelitis is found which after several weeks or months undergoes resolution, without chronic disability as a rule.

A second type of acute hematogenous osteomyelitis occurs in the newborn, however, a *severe form*, in which the systemic evidences of a violent infection usher in the syndrome and the local disease makes its appearance as a complication of his condition. In these cases the onset is usually early in the newborn period, with the advent of fever, usually marked and often of a septic type. The concomitant symptoms will depend to a large extent upon the primary disease process which constitutes the portal of entry of the blood stream infection. In the newborn the umbilicus is a common site and here local evidences of an omphalitis may be present with redness, induration and purulent discharge. It is true, however, that occasionally there may be no definite evidence of inflammation externally at the time of examination, and still a thrombophlebitis of the umbilical vessels may be present as the source of a septicemia which gained entrance through the cord stump. The respiratory tract may not uncommonly be the source of septicemia in the newborn, and here again marked evidences of involvement locally may be lacking on admission. On the other hand, suppurative complications of an upper respiratory tract infection such as an otitis media or sinusitis may be present, or a definite pneumonia may be found. The skin or, less commonly perhaps, the urinary tract may be the site of a pyogenic infection which may result in septicemia. The bacteriology of these cases is quite variable, streptococci (nonhemolytic, and hemolytic), staphylococci, pneumococci or other

pyogenic organisms may be found and are usually isolated from the blood stream without too great difficulty. The process is a malignant one, is often associated with icterus and hemorrhagic manifestations and requires active and often heroic therapy. The mortality, even with modern therapy, is high. Localization in the bone occurs relatively late in the course of the illness and may be discovered accidentally in the course of routine x-ray examination, or may manifest itself by the formation of local soft tissue abscesses which direct the observer's attention to the underlying bone. The focus may be single or multiple areas may develop, and in this form of osteomyelitis in the newborn the bone lesion is more apt to become chronic with the development of sequestra and sinus formation, and when large segments of bone are destroyed, as in the case of the head of a long bone, may result in chronic disability. Even in the severe form of osteomyelitis in the newborn, however, the degree of restoration of the involved bone to normal is often surprising.

In the Older Infant—In the older infant the early symptomatology is also dominated by the septicemic symptoms. The onset is usually abrupt, often with high fever, and not uncommonly with respiratory tract symptoms. In a few instances a history of trauma to the area later involved is elicited, but since mild trauma is so common in infancy it is difficult to evaluate the importance of this factor in a given case. An infectious diarrhea or a furunculosis of the skin may be the initiating symptoms. After a few days the infant begins to evidence disability of an extremity, there is frequent crying as though in pain, particularly upon handling, and soon it is noted that an extremity is held very quietly, usually in a position of rest. Upon attempts at passive motion of this extremity pain is elicited, and at times a tender point over a metaphysis may be demonstrated on careful examination. Usually the joints are uninvolved and their free mobility can be demonstrated on careful examination. Soon an enlargement of the metaphysis can be demonstrated on careful palpation, and as time goes on a sense of deep fluctuation may be felt in this region. Then as a rule a soft tissue abscess begins to develop and usually will enlarge and approach the surface rapidly. In the acute stage the infant is prostrated, severely ill, and becomes rapidly dehydrated. Blood culture during this period will usually yield the invading organisms. X-ray evidence of bone destruction may be found in seven to ten days after the onset. When localization in the soft tissue has become well developed, usually two to three weeks after the onset, the general symptoms tend to ameliorate and the infant begins to eat, look better and gain weight. If recovery from the acute septic phase occurs the prognosis is good in this age group. The bone lesion seldom becomes chronic and complete restoration to normal is the rule.

Therapy—The treatment of acute hematogenous osteomyelitis in infancy may be divided into medical and surgical therapy. Medical

therapy is concerned essentially with supportive measures to combat dehydration and toxemia, and specific chemotherapy aimed at destroying the invading organism. Surgical therapy is concerned with handling the local bone involvement.

In acute hematogenous osteomyelitis in young infants the disease process is a severe septicemia and its therapy is the all-important phase. Dehydration must be combated by the administration of parenteral fluid. This is usually given by the intravenous route, a cannula being inserted in one of the superficial veins after cutting down in the vessel and fluid being administered by slow intravenous drip. Normal saline, dextrose, Hartman's solution, whole blood and specific antisera are administered in this manner. Cannulae may safely be left in place for several days. Bone marrow infusions should not be attempted in this type of case.

Chemotherapy is an extremely important phase of the management. In our present state of knowledge penicillin offers the best choice of therapy. It may be administered in a single, rather large initial intravenous dose, followed by divided intramuscular doses at three-hour intervals throughout the septic period. The individual dosage will depend upon the severity of the infection, 30,000 to 50,000 units being administered in an initial dose, and 5000 to 20,000 units intramuscularly every three hours thereafter. The drug is extremely effective against most of the organisms encountered in acute hematogenous osteomyelitis and may be given with a high degree of safety.

The sulfonamide drugs may be used either alone or in combination with penicillin. Sulfathiazole or sulfadiazine will be found to be the most effective and best tolerated. They must be used in large doses and the usual precautions must be followed regarding their effect on blood destruction and urinary excretion. We have found it advantageous to alternate the drugs in individual cases. As a general rule from 0.1 to 0.2 gm (1.5 to 3 grains) per pound of body weight per day may be administered. The drug is usually given by mouth but in specific instances in which vomiting occurs or the infant is very toxic it may be given intravenously as its sodium salt. In some of these highly toxic infants with a persistent septicemia the drug must be given over long periods of time and in relatively enormous amounts. Most infants tolerate such long-continued therapy very well and show little deleterious effect. Repeated intravenous blood transfusions and high doses of vitamins must be administered under these circumstances.

Local therapy of the bone lesion consists in immobilization, local hot wet dressings and the incision and drainage of soft tissue abscesses when they appear. Surgery to the bone should be held to an absolute minimum, incision of the periosteum over a subperiosteal abscess should usually constitute the maximum handling permissible. Local use of penicillin or sulfonamide may be of aid after incision.

SUMMARY

Acute osteomyelitis of hematogenous origin in infancy is essentially a septicemia with localization in one or more bones. The local lesion in the bone in this age group is frequently much less malignant than that seen in older children or adults, inasmuch as chronic osteomyelitis with sequestration and chronic discharging sinuses are much less frequently seen. In fact, in these young children there is a strong tendency for the lesions to undergo complete resolution with eventual restitution of the bone to approximately normal condition.

To speak of acute osteomyelitis in infancy or in the newborn period as a benign disease is not accurate, however. The nature of the illness will depend largely upon the invading organisms producing the septicemia, the degree and severity of the blood stream infection, and the nature of the primary illness acting as the portal of entry.

Finally, acute hematogenous osteomyelitis in infancy should be considered a pediatric medical condition and the pediatrician should be prepared to assume its supervision. The surgeon and the orthopedist should act in the capacity of consultants, since active surgery to the bone in the acute stage is probably detrimental rather than helpful. In the treatment active employment of penicillin and the sulfonamide drugs, particularly sulfadiazine and sulfathiazole, has proved most valuable.

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FLAT FEET IN CHILDREN

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MANY flat feet in children are normal. In fact, a considerable proportion of the human race has a very low structural arch. If the foot is flexible, has good muscle control, and the os calcis is not tilted into a varus or valgus position, the congenital hereditary or racial type of flatfoot will stand as much hard usage without producing pain or other disability as does the foot which we are accustomed to think of as having a normal arch (Fig. 21).

In the newborn infant the plantar surface of the normal foot is flat. This is true even though there may be an excellent bony arch. Until a child is about three years of age the portion of foot which subsequently becomes the longitudinal arch is filled with a pad of fat. As the infant grows older this fat pad shrinks.

Mild inversion of the forefoot of the child who is beginning to walk, a position commonly referred to as "pigeon toe," is a common cause of concern. In the absence of definite structural abnormality, muscular imbalance or congenital deformity, toeing-in should be regarded as a normal reaction on the part of the child. This calls into action the anterior and the posterior tibial and the short adductor muscles of the foot, and by using them, strength for the support of the arch is increased. Thus the normal, healthy child, without any instruction or assistance on the part of his elders, automatically goes about the business of strengthening the arches of his feet. Slight inversion of the forefoot should not be discouraged nor should any attempts be made to prevent it by means of braces, casts or other appliances. The more the child wiggles his toes, slightly inverts the forefoot, and engages in every manner of activity that requires the use of the muscles of the leg below the knee and the intrinsic muscles of the foot, the more he can be assured of satisfactory foot function later on in life.

Painful feet of children occur rarely. A low plantar arch does not appear to influence the incidence. Pain is indicative of the presence of inflammation, due to repeated trauma or to infection, muscles, the plantar fascia or the tarsal joints. Arthritis

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joints may cause severe disability. Arthritis in children may be the result of trauma or infection and may involve only one or all of the joints of the foot. The arthritic flatfoot has a lack of resiliency due to stiffness of the pericapsular ligaments and may be severely disabling.



Fig. 21—Congenital flat feet without eversion of os calcis or disturbance of weight-bearing alignment. Such feet are usually painless and function quite as well as do feet with the so-called normal arch.

Chronic strain, which may affect the muscles or the fascial support of the foot, occurs in patients who have had normal to high arches as well as in the patients whose feet are congenitally flat. This condition occurs most commonly in children who are overweight or in older patients who are physically sluggish, but it may be the result of a specific injury. The child who jumps or falls from a height, landing on his feet, projects the entire weight of his body against the support-

ing structures which span the longitudinal arches. This may result in acute sprain, pain and disability (Fig. 22)

Contrary to a common belief of the lay public and of many physicians, the foot with a very high arch is more often associated with pain and disability than is the simple flatfoot. Pain produced by so-called "*arch breakdown*" occurs most often in feet in which there is an adequate arch to begin with but some subsequent strain or injury results in a tear of the plantar fascia or of the capsule of the midtarsal joints. Marked muscular weakness of the supporting muscles may also follow protracted illness. If the high arch sags with the continuous strain placed upon the nonelastic supporting tissues, these structures may become edematous, tender and painful. This rarely occurs in the congenital flatfoot.

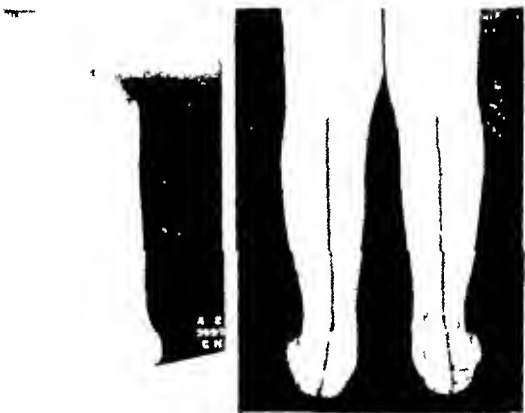


Fig. 22—Congenital flat feet with slight eversion of os calcis. This type of foot is usually not painful and functions quite well. However, the weight-bearing disalignment has been such to produce slight genu valgum deformity.

Many children are never permitted to walk without having their feet encased in stiff leather shoes. Rarely are these feet given the opportunity of adequate movement of the various segments. Little functional exercise is permitted the intrinsic muscles. These are muscles with attachments to the os calcis and to the metatarsal or phalangeal segments. The average adult has used these intrinsic foot muscles about as often as the muscles which, phylogenetically speaking, were intended to wiggle the ears. As a result of constant splinting of the human foot with leather shoes and an absence of consistent use of these intrinsic foot muscles they waste away until they no longer protect and support the various components of the foot.

The weight-bearing surfaces of the human foot function as a tripod. The posterior support of the tripod is the os calcis which is covered by a thick pad of mixed fat and fibrous tissue to protect against bruising and the strain of direct weight bearing. The anterior supports of the tripod are to be found over the head of the first metatarsal and the heads of the fourth and fifth metatarsal bones. When standing with the weight directly upon the foot, these three points should receive and support at least 90 per cent of the load. If both the intrinsic muscles of the foot and the muscles of the calf of the leg are strong and good foot posture is maintained, no direct weight will fall on the heads of the second and third metatarsal bones. If the metatarsal arch does pronate so that excessive weight is borne on the heads of the second and third metatarsals, pain in this region will follow. The underlying skin will become thickened. In this callus plantar warts may grow and become acutely painful. This breakdown of the so-called metatarsal arch may result in impingement of the interdigital nerves between the second and third metatarsal heads. Oft-repeated trauma to this nerve may produce a *vascular neuroma*. This condition may be severely disabling and if not alleviated by conservative treatment, surgical excision of the nerve segment is indicated. This is the explanation for some of the more acutely painful and intractable cases of what is commonly called "Morton's toe." If the muscles that control toe flexion are used strongly in walking, the weight strain is shared by the toes and metatarsalgia will occur rarely. Failure to use vigorously both the short muscles that are intrinsically present within the foot and also the long muscles to the toes so that the weight-bearing load is distributed in part to the very ends of the toes supplying the kick-off thrust when walking, is the primary reason for the so-called breakdown of an arch with the development of chronic foot strain and a secondary painful flat foot. Such a condition occurs very rarely in children but has its inception in childhood, if the child's feet are oversplinted and not given the opportunity of freedom of movement and exercise as he grows and develops.

A theory which has dominated both medical and lay opinions for many generations has been erroneously based upon the belief that the muscles and ligaments of the foot could be strengthened through *exercises* which were carried out for fifteen to thirty minutes each day, this is illogical. The psychological trauma attendant upon forcing a child, who is filled with nervous energy and wishes to be out with his friends on the playground, to sit for half an hour every day and pick up marbles with his toes, or walk around the living room rug for a similar period of time with the feet inverted, has little therapeutic value. This is mere "toe twiddling." The overanxious mother may be soothed with the thought that she is actually doing something for her child when she "cracks the whip" and insists that he go through this routine, but the arches of her child's feet will be

helped very little. The average painless, flexible flatfoot without marked ankle roll or eversion merely needs a good pair of oxford shoes and opportunity of complete freedom to exercise the muscle through normal play activity.

Children should be not only permitted but encouraged to play with their feet bare when the weather permits and the terrain is favorable. In the sand at the beach, in the clean grass of a yard or park or in the soft dirt of a plowed field, the bare foot will automatically respond to contact with nontraumatizing surfaces by movement of all of the joints throughout the foot and repeated contraction and relaxation of the various muscles. Unfortunately, children who live in a city have little opportunity for this untrammelled type of recreation. They spend most of their waking hours on hard floors, hard sidewalks, or hard pavements. The human foot was not planned for surfaces such as these. Under these circumstances the foot must be protected. This protection, however, is required principally for the portion of the foot which makes direct contact with the surfaces upon which the child walks. The sole and heel of the shoe are most important from the standpoint of protecting and splinting the foot.

Oxfords or *sandals* with a strong leather sole may afford adequate protection insofar as the arch and the various components of the weight-bearing elements of the foot are concerned. The footwear should allow ample room for the toes, with adequate width, length and depth to the vamp to avoid constriction or interference with circulation. The heel portion of the shoe should fit snugly. The counter should be reinforced and should extend forward to the region of the scaphoid bone. Eversion of the heel may be corrected and weight evenly distributed from the heel down the outer side of the foot and then across from the base of the fourth and fifth toes to the base of the first toe by using a long orthopedic or Thomas heel, wedged $\frac{1}{8}$ inch on the inner side (Fig. 23).

For generations mothers and fathers have told their children that they should wear *high-top shoes*. Many doctors have given the same information to their patients. This is based upon the fallacious theory that the ankle will become weakened if it is not splinted by the shoe, or that a weak ankle will be further injured unless supported. Any student of physiology or of anatomy knows that muscles, bones and tendons become strong through usage and not through immobilization. Splints are of value merely to permit torn structures to repair or broken bones to knit. Continuous splinting of a perfectly normal arm or leg will lead to wasting of all of the structures with shrinkage of muscles, atrophy of bone, and weakening of ligaments. A high-top shoe is definitely a splint to the ankle. The longer that it is worn inhibiting completely free movement of tendons and hence interfering with exercise of the muscles, the weaker the ankle will become. Structural support in almost every instance of weak foot or painful flatfoot

or eversion foot due to rolling of the os calcis, can be obtained in an oxford with a strong leather sole, a long counter, Thomas heel and an inner side wedge. The use of high-top shoes in children who are growing and whose structures must develop and become strong through usage is a vicious tradition.

Knock-knees sometimes result from the strain that is produced upon the medial collateral ligaments of the knee when the weight is borne constantly upon feet which are pronated and everted. Oxford shoes with Thomas heels wedged $\frac{1}{4}$ inch on the inner side, which support the arches and correct the os calcis roll, will relieve this strain. If

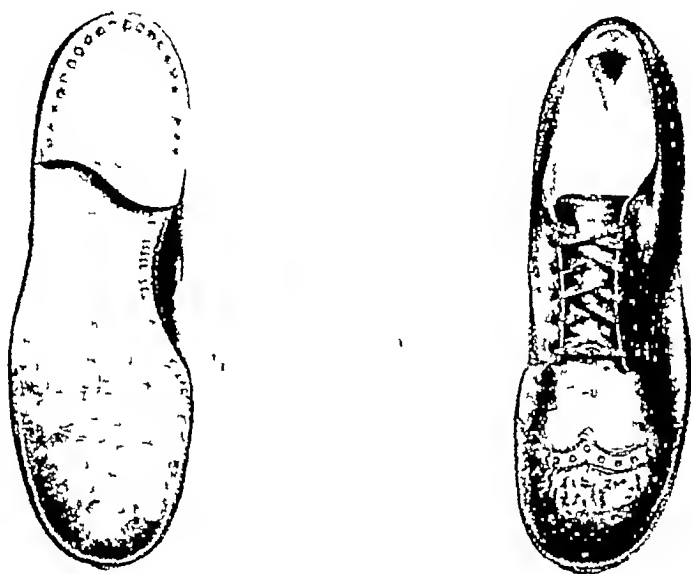


Fig 23 —Straight last, stiff soled oxfords with Thomas heel. This heel is wedged varying amounts on the medial side, depending upon the extent of os calcis eversion.

these orthopedic supports are maintained throughout the years of growth the genu valgum will slowly correct (Fig 24).

Flat feet are very common among people of primitive races. Some entire tribes have never worn shoes from the beginning of time until the present day. Among such people painful feet exist only as a result of specific injuries. Many of the foot disabilities of civilized people result from overprotection of the feet by encasing them in shoes for generation after generation. Even in the most correctly built shoes the intrinsic muscles of the feet receive minimal functional exercise.

Until a few years ago metal plates to support the arch and correct the ankle roll and eversion of the os calcis were prescribed for most patients who complained of foot pain. In the treatment of painful flat

feet, chronic fatigue, or arch breakdown these plates were necessary because during much of that period orthopedic shoes which afforded good support to weak feet were not readily obtainable. Today such shoes are supplied by most of the retail stores and metal plates are rarely prescribed by the modern orthopedic surgeon.

For the acutely painful flatfoot associated with marked disturbance of weight-bearing alignment, the protection afforded by orthopedic shoes may not be adequate. These feet may require surgical treatment. Following a fracture which extends into one of the midtarsal joints a



Fig 24—Complete pronation with moderate eversion of the heel which is more marked in the right than in the left leg. As a result a fairly marked genu valgum deformity has developed. By wearing good orthopedic oxfords with a Thomas heel wedged $\frac{1}{4}$ inch on the inner side complete correction of this genu valgum should be obtained in a period of about three years.

severe sprain in the midportion of the foot, or because of rigid or spastic pes planus associated with congenital or developmental fusion between the os calcis and the cuboid or scaphoid bones, pain upon weight bearing may be constant and produce great disability. Flatfoot associated with peroneal muscle spasm and pain is commonly caused by one of these lesions. A few of these patients may be relieved following manipulation of the foot under an anesthetic and the application of a walking plaster cast to maintain a position of inversion for three to six weeks. If this conservative procedure merely affords tem-

porary relief an arthrodesis of the midtarsal joints is indicated (Fig 25)

Overanxious mothers who have read too much in the lay press about the dreadful results of neglect of their children's feet require



Fig 25—*Extreme weight-bearing disalignment with pes valgus* Feet such as these cannot be corrected adequately with any type of shoe or shoe correction. An operation to restore the arch by means of a midtarsal arthrodesis is definitely indicated.

more reassurance than their children with supposedly flat feet need treatment. Marked anxiety on the part of mothers may be harmful to the child and should be alleviated by explaining the true situation and by calm reassurance.

FEARS IN CHILDREN

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CHILDREN are born with potentialities for growth and development which determine their general growth patterns. There is also present at birth a well developed and functioning mechanism through which individuals respond to their environment and in infancy this response is entirely in terms of feeling. Under some conditions the infant is satisfied and complacent and under others he feels scared or resentful. While the degree of response varies with individual babies, the character is exactly the same if provoking conditions are the same.

All behavior is in terms of habit. The baby from birth forms the habit of responding in terms of fear and resentment on the one hand or satisfaction and complacency on the other hand. Since conditions for mental growth are never perfect every infant responds with excessive fears and resentments and we can only hope that the latter will predominate.

The Nature of Fear—Fear and resentment are important emotions representing the instinct of self-preservation. Justifiable fears and hates which are conscious, understood and intelligently managed make up an important part of a healthy mind, but when the whole personality is controlled by fears and hates we have a mentally ill individual. The problem of rearing children, then, becomes one of allowing them to grow up with confidence and resulting self-reliance rather than with extreme fears which will dominate their behavior.

As already intimated, fear and hate are closely allied emotions and neither can be considered entirely alone. A baby is probably scared when he comes into the world and is angry soon afterwards and throughout life the one emotion or the other may predominate when threats or insults arise but they are seldom far apart.

Fears in the Newborn Infant and Young Child.—Babies have two specific fear reactions at birth—loud noises and sense of falling. In addition, restriction of movement, sense of suffocation, hunger and pain, uncertainty and lack of security are conditions which illicit the same response.

Security is the feeling which is given an infant from birth by parents who wanted a child, accept him as he is, no alterations being necessary, and who allow him to grow up according to his own patterns and get satisfaction out of his own abilities. Insecurity is fos-

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tered by the failure of parents, especially the mother, to make an infant feel he is wanted and accepted as he is and it is further stimulated by standards of behavior which the child is unable to meet. With these general principles in mind let us enumerate some of the common fears which have been observed by pediatricians who observe growth and development of children, and by psychiatrists who study mental ill health

Before birth infants are fed continuously, kept warm, comfortable and secure. Birth comes as a sudden shock and this extreme change in environment releases all of the reactions of self-preservation. For this reason fears and resentments are easily and frequently stimulated in the newborn. The newborn is frightened if he is away from his mother for more than short periods and should, therefore, be with her most of the time. When this is not practical babies are less apprehensive if their crying is relieved by being taken up by nurses. More security is provided by breast feeding than by any other single means and when this is not possible, the infant has less anxieties if he is *carried* to his mother at each feeding period in order that she may hold and fondle him while giving him the bottle.

Since an infant acts the way he feels and because he is not able to wait for the gratification of his wants without feeling scared or resentful, his emotional needs require careful consideration. These requirements for mental growth do not conflict in any way, in fact they are part and parcel with his needs of physical growth. Nearly all babies are born with a fairly regular waking and sleeping rhythm which may be used as a basis for their food schedules. This schedule, of course, is never exact but the intervals are usually longer during the night than during the day and they usually approximate three, three and one-half or four hours. Feeding infants when they are hungry (according to their individual rhythm) fosters physical growth and adds to their comfort and security. A baby who is allowed to cry for an hour five and six times a day because of hunger is experiencing serious anxieties.

Anxieties are often stimulated by unnecessary and painful enemas as well as forced feeding, as illustrated in the following case report.

A 2½ year old boy was brought for examination as a food and bowel problem. He was a small youngster with small bones and muscles and weighing 22 pounds. The physical examination, however, was entirely negative. He never ate more than 60 per cent as much as the average child, but he was an alert, smart, active, normal appearing boy. His intelligent and cooperative parents were worried over his health and concentrated on his food and bowel habits. His mother stated that she often wanted to give him affection but thought it was not the right thing to do. She also thought that he must have a bowel movement every day or he would get sick. About three months before the examination the boy had a hard stool and cried. Following this experience he cried when put on the toilet and his mother used suppositories daily "to help him." Finally he refused to go to the toilet and would lie on the floor, obviously trying to hold back a

stool and for this behavior his mother spanked him. He then began to cry more frequently refused to play outside unless his mother went with him and would say "I am scared" The patient would not say what he was afraid of and obviously did not know

This patient was an insecure boy whose emotional needs were not supplied. In addition his mother lost her temper and tried to force him to eat and move his bowels. This deprived him of three vital emotional needs (satisfaction in digestion, elimination and motherly love), and made him apprehensive. The pain of a bowel movement, which would not disturb most children, was frightening to him. His mother was asked to rock him daily and give him praise and affection. She also omitted the unnecessary punishment, forced feeding and forced bowel movements. The patient improved rapidly and at the end of a month he was feeding himself and was going to the toilet voluntarily. He also began playing outside for short periods without his mother.

Many parents are ambitious to establish bowel training at an early age, before the infant is equipped to take on that important responsibility. Bowel training is best initiated when a child is old enough to appreciate its significance and wants to take that responsibility. It, therefore, should not be begun before 9 months of age and in many children one year of age is a better time. Whenever a mother reports she is having difficulty in her training, even though she began at the proper time, we know that she has been making too great an effort to force training rapidly and the child is too frightened or resentful to accept responsibility. If she stops her efforts for a month and then begins again more slowly she will likely succeed.

An infant is most secure when cared for by its mother in the same home. Fears which were stimulated by changes in the environment of babies are illustrated by the following cases. A 4 months old baby cried on four succeeding days when his mother left him with friends while she was visiting. During these periods his pupils were large and he showed every sign of fear. When his mother returned he stopped crying and was comfortable again. A 9 months old baby cried when put to bed and woke up crying for several days after her mother had changed the furniture in her room and placed her bed in a different position. The crying spells subsided when her bed was returned to its old position.

Infants cry out in their sleep and apparently have disturbing dreams after being frightened during the day by falls, loud noises, inoculations and other disturbing experiences. These anxieties quiet down more quickly if the baby is rocked before he is put to bed and if his mother goes to his bed immediately, and if necessary holds him for a while, every time he wakes up crying.

A 2 year old girl developed fears of lightning and thunder because while visiting her grandparents and sleeping in a strange bed in a strange room there was a storm. She had not been disturbed by storms

previously but the anxieties produced by the strange environment, in addition to the thunder and lightning, were sufficient to leave her frightened of storms afterward

Children commonly develop fears of their own parents, especially during the discipline period. When parents expect instant obedience and adult behavior of their children, and especially if they lose their tempers and convince their children that they are bad and no good because they do not meet these impossible standards of conduct, the children come to fear them. The resulting fear, hate and sense of guilt contribute a great deal to the neurosis of the preadolescent and adult. When we analyze the "nervousness" of our adolescent and adult patients, we find that it is made up largely of these emotional disturbances which were acquired in early childhood.

Anxieties develop in the minds of young children when they are separated from their parents and are cared for by strangers. The following case is illustrative.

An 18 month¹ old girl was left with her grandparents, who lived in a dark apartment, being removed from her own light, sunny home. Both of her parents left town suddenly after one of their periodic quarrels. When the little girl was seen the following afternoon, the grandparents reported that she had cried the greater part of the previous night and that they had been forced to carry her most of the time since her arrival. The patient was obviously nearly exhausted and was so frightened that she could not sleep. She was placed in a hospital where she was held and rocked by competent student nurses. She improved in a few hours and in a couple of days she stopped crying and was content.

This case not only illustrates a source of anxiety but also the value of well trained nurses who have the proper attitude towards children.

Medical Fears.—Of special interest to the physician are the fears which children acquire from illness and various medical procedures. Since the whole subject of illness is associated with death and because of the popular belief that illness is associated with punishment, it is not surprising when children feel that illness is punishment for being bad. Cardiac patients with anxieties often state that they got heart disease because they ran around too much and were bad. Diabetic patients often feel their illness is due to disobeying their parents by eating too much sugar. Children are often apprehensive when they are ill because parents tell them "It serves you right, you left your rubbers off yesterday and, therefore, you are sick. If you would mind your mother you wouldn't get sick."

We see many severe anxieties in children following hospitalization. The reason for these fears can be understood when we describe that experience which is commonplace to us but very serious in the minds of children—namely, tonsillectomy. Often parents prevaricate to their children and tell them they are going to a party and can have all the ice cream they want, and so on. With that pleasant anticipation the child arrives at the hospital. He notes the curious odors in the hospital

and does not understand the admittance procedures. He is taken upstairs and put to bed. If he is a charity patient his parents are told to go home. The patient finds himself surrounded by unusual procedures, people dressed in uniforms and, too often no one pays any particular attention to him. He realizes by this time that his parents have not told him the truth and he, therefore loses his feeling of security in them. In addition, he is surrounded by uncertainty, the other condition which always stimulates fear. Later he may be told that he is not going to be hurt and his ear is pierced for a blood test. Finally he is placed in a chair or hospital cart and taken up in an elevator to the operating room, where the odors are strong. He observes shiny instruments and operating room apparatus and everyone is dressed like a ghost. Even though he is very fearful often operating room procedures forbid anyone to talk to him or explain what is going to happen. He is placed on an operating table strapped down and held while the anesthetic is being administered. Even though the anesthetic is given carefully, there is a certain amount of strangulation or suffocation.

When the patient awakens he feels sick, his parents may not be present, and he is liable to be criticized if he whimpers or gets a spot on the bed. We frequently see children who are very nervous (meaning frightened) following this procedure. Every child is profoundly affected by it.

It is sometimes necessary to perform operations and hurt children but the amount of anxiety resulting from these experiences can be reduced fully 75 per cent by following a few simple rules. The first and the most important of these is never to lie to a child. He can be told what is going to happen to him and every step in the process can be carefully explained. When this is done and the patient finds that everything is being done as was anticipated, he retains the feeling of security in his parents and confidence in his physician. When he is assured that he is going to be all right again in a week, he believes this to be true and can experience the unpleasantness of the operation without undue fear.

The ideas which a child may get when he is not properly instructed before he is taken to a hospital are illustrated in the history of an 11 year old boy who was taken from a small town to a large city for examination and the beginning of orthodontia. He refused to allow the physician to examine him and cried a great deal in the hospital. When seen his pupils were large and he was obviously in distress. When he was asked what he was afraid of he began to cry and said, "What are you going to do to me?" He was urged to state what he thought might be done to him. He stated that "drafts" were going to be placed in his jaws and that a "draft was a hole." He overheard the physician at home talking to his parents and the word "graft," was used. The patient interpreted this as a draft and since drafts are caused by openings he concluded that they were going to put holes in his jaws so that air could get through. When the therapeutic procedures were explained to him his anxiety disappeared and he became a very cooperative patient.

A 7 year old boy sat up and said to his physician, "You are a liar, I hate you," after the physician said he would not hurt him and then did a paracentesis. A 9 year old girl complained about her parents, saying, "I will never forgive them for lying to me when I had my tonsils out." Anxieties and resentments of this kind can always be avoided by the proper psychological preparation of a child for any operative work. Children soon learn whether parents and physicians tell them the truth. Once their confidence is obtained they will submit to the painful procedures with little difficulty.

Car Sickness—We see many children with car sickness, either automobile or streetcar. This type of illness is never found in infants and usually develops at two or three years of age. Interrogation of these patients will reveal that they fear an accident. They imagine that there is going to be an accident and that they will be hurt. This fear causes nausea, headaches and finally vomiting. The children will not develop car sickness if someone plays with them and keeps them distracted while they are riding. They will soon recover if the nature of their difficulties is explained to them and they are assured it is not necessary for them to get sick.

Visual Disturbances—Beginning with the preadolescent period and increasing with frequency into adulthood, we see visual disturbances which are on a functional basis apparently due to spasm of the blood vessels. It is possible to get tubular vision, decreased vision or hemianopsia. The following cases are illustrations.

Frank R., a 10 year old boy, came for examination with a complaint that he could only see objects directly in front of him. This condition developed on Christmas Eve. He was playing with his toys when suddenly the visual difficulty came upon him. A careful history indicated that he was a fearful boy—he thought he was bad and was reared with the idea that if he was bad Santa Claus would not bring him Christmas presents. On the evening of the onset of the trouble he suddenly became very fearful that someone was after him and thought a burglar was looking into the window at him. When he was able to analyze his fears with the help of a physician, the difficulty disappeared and has not recurred although nearly ten years have passed.

Eva B., a 14 year old girl, suddenly "went blind" after class in high school. She went to the school nurse and later was carefully examined by an ophthalmologist, who found nothing wrong with her eyes. The first attack lasted about thirty minutes and she had many subsequent attacks of shorter duration. Eva was a highly intelligent but emotionally disturbed adolescent girl. With psychiatric help she learned that the diminution of vision occurred when she became frightened and confused. She did not lose all of her vision (these patients never become totally blind) as evidenced by the fact that she went to the school nurse without assistance from anyone. The first attack was precipitated by a "bawling out" from her teacher whom she felt had wrongly accused her of doing inaccurate work.

Anxieties in Preadolescent Children—We frequently see serious anxieties in the minds of preadolescent boys and girls which closely resemble the anxiety neurosis of the adult. The patients usually come for examination because of the fear that they will become ill and die.

Their complaints are not unlike those of the adult neurotic abdominal pain, nausea, choking spells, constriction of the chest, rapid heart, weakness and so on. They are afraid that these symptoms mean serious illness and develop a typical panic. The following case is illustrative.

A 9½ year old girl came for examination for "spells" during which she cried bitterly, complained of a severe headache and asked repeatedly "Am I going to die?" These attacks began three months following the death of a younger brother with meningitis. She developed her first panic when playing cards with another brother and sister while her mother had gone to the store. Her mother had told her to do a certain amount of housework while she was away but she played instead. She felt fearful and guilty for not obeying her mother at the time the first panic developed.

In analyzing this case, the following factors came to light. Her mother stated frankly that she had never felt towards the patient as she had towards the other children and that the baby who had died was her favorite. The patient had been required to watch over the little boy who died and was naturally very resentful towards him. The patient also had strong resentment towards her mother and the usual jealousy towards the other children. She had strict rearing and was taught that it was bad and wrong to hate anyone. She felt very guilty after her brother died because she hated him. When these hates, jealousies and sense of guilt came into her mind she became frightened and confused causing the headache and the resulting panics in which she believed she was developing meningitis.

In analyzing a series of these anxieties in preadolescent children, one finds that in nearly all cases the patients were rejected by their parents, that is, either the patient was hated by his parents or there was something about the patient which the parent was unable to accept. We usually find that the patients have had a rigid program during infancy and during the disciplinary period and that they have not had an adequate amount of praise and affection. They are nearly always very good children, meaning that they are very apprehensive youngsters. There is nearly always a precipitating event, such as the death of the younger brother in the above case. Fear or hate is commonly the anxiety which initiates the emotional upheaval causing functional symptoms. Acute anxieties of this kind begin with the preadolescent period because that is the period of rapid development of conscience. These individuals are nearly always very sensitive, probably from birth.

Anxieties About Sex—Parents still assume that children have no sex feelings, interests or curiosity, even though it has been demonstrated scientifically to the contrary a great many times. The seriousness of sex fears which develop in the minds of children depend upon the attitude which is taken towards the whole subject by parents. While there is probably little differentiation between the rectal and genital regions of young infants, the possibility exists that the mother with a cleanliness complex, who overstimulates this area in changing the baby and who gives painful enemas, may create confusing ideas in the minds of babies. We see evidence of the frightening of children

every day in practice when mothers bring their babies to the office for routine examinations. At four months of age babies grasp objects and when they are undressed eventually grasp the genitals. Mothers pull their hands away, possibly give them a slap and may say, "naughty-naughty." This is often the first behavior of the infant which meets his mother's disapproval and is the first time that she becomes apprehensive about his future behavior. When the child is old enough to understand, he is commonly taught that touching himself or showing any normal curiosity about the difference between boys and girls or where babies come from is bad and dirty. Fears produced by this frustration of the youngster may cause serious anxiety later in life. It is illustrated by the following case.

A 19 year old girl developed a washing complex, that is, she took eight to ten baths per day, refused to eat and complained that she was dirty. She lost a great deal of weight, developed generalized dermatitis from the bathing and became mentally ill. From prolonged psychiatric study and help she traced her anxieties to an experience she had when she was about three years of age. She was caught in the garage with two boys, four and five years of age, with their clothes off and examining each other. She was severely chastised by her mother and told that she was a dirty, nasty girl. Following that experience she was guarded carefully and told many times by her mother how bad and dirty it was to touch herself. She grew up a timid, shut-in girl who managed to finish high school. About this time she fell deeply in love. She was unable to reconcile normal love feelings with the severe teaching she had during her childhood. This frustration and confusion caused her to feel she was dirty and bad and she developed the compulsion to baths.

One sees a great many children with less severe but serious anxieties about sex. A 9 year old boy was convinced that there was something the matter with his genitals and became a difficult problem at home and in school. We see cases of exhibitionism and frigidity due to suppression of sex interest and feelings. When boys and girls arrive at adolescence, that period of life when sex wishes are the strongest, and they have been convinced that their sex wishes and feelings are abnormal, they try to force those normal feelings out of their minds. The writer has seen four girls, three of them juniors in high school and one a sophomore in college, who were convinced that they were pregnant but who did not know that sex relations were necessary. They were all scared girls. One had the idea that she became pregnant from kissing boys and the other two believed their pregnancy was due to sex wishes. A 16 year old boy was arrested for exhibitionism. He was a very mature and well developed boy, who had been desperately trying to keep sex wishes out of his mind and had apparently succeeded in doing so. As a result, however, he had developed the compulsive behavior exhibitionism.

In studying the fears of children we find the basis for much of the mental ill health of adults and discover the principles for rearing children in order that they will have mental health.

CONVULSIONS IN INFANCY AND CHILDHOOD

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It is believed by the laity and even by some physicians that there is a subtle difference between the convulsions occurring in infancy and those which appear for the first time in childhood or in adult life. There is an even more deeply rooted belief that those convulsions of infancy or childhood which are associated with a feverish illness have no serious connotation and that those which take place apparently spontaneously are evidence of a sinister disease called epilepsy. With our present limitation of knowledge there is no justification for the common concept that there is a disease of epilepsy which is hereditary and intractable and which leads to inevitable mental deterioration. There is no known difference in any one convulsion from any other no matter whether it is associated with any recognizable disease or not. The true pathogenesis of any convulsion is still unknown to medicine, and there is no known cellular pathology for a convulsion itself. A convulsion, solitary or repeated, is a symptom and not a disease.

An honest admission of the depth of medical ignorance of the true pathogenesis of any convulsion is necessary not only for the sake of intellectual honesty but also for successful attempts at treatment.

It has long been postulated on theoretical grounds that any human brain with an adequate and specific stimulus can be induced to undergo widespread "inhibition" in the upper physiological levels and to discharge explosively through the motor pathway. Shock therapy for psychoses has demonstrated clinically that this theoretical concept is true.

There is probably no one, no matter how normal, who at some time in his life has not experienced an isolated, spontaneous jerk of a finger or of a limb. These jerkings are presumably the result of a sudden, involuntary and uncontrolled discharge of a group of neurons in the motor cortex. These jerks are larval fits.

The irregular, restless, muscular movements of a young infant are of the same quality. They too are presumably the result of the irregular, explosive discharge of groups of neurons in the growing motor cortex. As the infant grows, these irregular jerkings disappear to be replaced by smooth voluntary movements of the limbs. In order to achieve this, synchronous inhibitions of adjacent regions of the cortex

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presumably develop. If this does not come, the child retains into adult life the bilateral spastic movements with cortical overflow which are normal in infancy. Such a person is then clinically described as having one of the various forms of *congenital spastic paresis*.

In a major convulsion the child or adult suddenly and for a short time returns to the state of irregular jerking movements of an infant. These are accompanied by complete loss of consciousness and complete loss of normal postural tone. The irregular movements of the fit are more rapid and more violent than the irregular movements of an infant, but their irregularity of pattern is the same.

In *Sydenham's chorea* the same irregular discharges from the cortex down the motor pathway are the characteristic features of the disease. In that sense, choreiform movements are long-continued, convulsive jerkings arising finally at the cortical level.

The various forms of convulsive attacks can be organized for description in the order of their extent. If a sudden involuntary discharge of a group of cortical neurons which produces the sudden jerking of a finger proceeds in procession over groups of adjacent neurons, there appears the march of movement up a limb from its periphery to its insertion without loss of consciousness. This is the classical *localized convulsion* of Hughlings Jackson and of Bravais.

In a *minor convulsion* there is a sudden, complete inhibition of the cortex with lightning interruption of consciousness, but without loss of postural tone. There is little muscular movement, and that usually only of the eyes, and there is no falling.

In an *akinetie major convulsion* there is sudden inhibition of the cortex and sudden loss of postural tone, but no phase of explosive discharge. The victim is suddenly unconscious and suddenly falls but has no involuntary muscular movements.

In a *major convulsion* there is sudden inhibition of the cortex and sudden loss of postural tone so that the person is unconscious and falls. Then the irregular, explosive discharge of the cortical neurons down the motor pathway leads to the irregular clonic movements characteristic of the classical major seizure.

In the person with spontaneous convulsive attacks of any clinical variety the threshold for apparently spontaneous inhibition and discharge is less than in the normal person. The level of this threshold varies greatly among people subject to attacks. All that can be said at present, however, is that there is a different threshold for inhibition and discharge of the different levels of the brain in people who are normal and those who have convulsions. No specific anatomical or permanent physiological differences have yet been described.

Most children pass quietly through the feverish illnesses of childhood but some have major convulsions when their temperature is high. It is the custom in pediatrics to call these attacks *febrile convulsions* and to assume that they are no indication that other similar at-

attacks may appear in the future unassociated with fever. However, a child who has had even one convulsion in his life and that associated with a high temperature, has by that token demonstrated that his cortex is less stable than that of his fellows. His threshold for discharge is lower than the accepted normal. No essential and absolute objective difference has ever been demonstrated between the child who has no attacks at any time in his life, the child who has attacks only with fever, and the child who has attacks apparently spontaneously, apart from the occurrence of the convulsions themselves.

It is clinically true that from 15 to 20 per cent of children who have attacks in childhood associated with fever have spontaneous attacks later in their life.

It is often assumed that an *electroencephalogram* objectively and absolutely will separate these three groups each from the other. It is also widely believed that such a tracing will determine with absolute accuracy whether or not the child who has had convulsions with fever is liable to spontaneous attacks in the future. These beliefs are unjustified in practice. An electroencephalogram is a visible record of the electrical discharges which are concomitant with cortical cellular activity. It is obviously, however, a record of only one phase of this cellular activity. The electrical discharges of the cortex of a child less than 5 years old are so often so irregular that it is not possible with assurance accurately to say whether such a record is an indication of a proclivity to spontaneous discharges or not.

Frequently a young child is seen by a neurologist for final decision as to whether or not he has "epilepsy." This is often done with the belief that the decision will in great part rest on the electroencephalographic tracing.

Despite the knowledge of cortical activity in normal action and in diseases of the brain that has been gained by the study of electroencephalograms, the final decision in every case of spontaneous convulsions rests on an accurate history of the attack and the details of its occurrence and not solely on the record of the cortical electrical discharges.

When an infant has a sudden and spontaneous loss of consciousness with irregular muscular movement, the attack is frequently diagnosed as being due to tetany or hypoglycemia. Even without the estimation of the blood sugar or of the serum calcium and phosphorus, without which either diagnosis is unjustified, an accurate description of the details of the attacks should immediately separate them from true major convulsions.

A type of major convulsions in young infants which is frequently not recognized as such is one in which there is a sudden forward dropping of the head with adduction and flexion of the arms. These attacks are extremely brief and tend to occur in bursts. They are really *lightning major convulsions*. They are most common in chil-

dren less than 2 years old They are notoriously difficult completely to control and are most often found in association with severe degrees of cerebral agenesis and mental retardation

A variation of minor convulsions difficult at first accurately to diagnose is sometimes found in children from 3 to 6 years old In this the usual minor attack may be very seldom seen The child is usually brought to the physician because of sudden unsteadiness This ataxia is of the trunk and of the legs It develops suddenly without any associated signs of increased intracranial pressure, but it is sometimes difficult to distinguish the true diagnosis from that of a tumor of the pons Frequently such a child has in addition an aphasia which gives the appearance of partial deafness and this coupled with severe ataxia gives added weight to the erroneous diagnosis of tumor of the posterior fossa This whole picture usually remains unaltered by medicine for some months, then may cease as suddenly as it first appeared This variation is probably most accurately described as *epilepsia minoris continuans*

A child may have a number of *akinetie major attacks* before a major attack with movement first appears These akinetic attacks are often falsely regarded as attacks of syncope This mistake is even more prone to occur if the attack of unconsciousness is preceded by a painful stimulus or a distressing experience A healthy child, however, very seldom faints Indeed it is very rare to find attacks of syncope in children even with severe degrees of congenital or acquired heart disease The speed of onset of unconsciousness in an akinetic major attack immediately distinguishes it from true syncope

It has also to be remembered that children may have a series of local or lateralized attacks, almost Jacksonian in type, as the introductory phase before true major attacks with universal movement first occur In this respect children differ from adults For this reason the diagnosis of *Jacksonian convulsions* in children should always be reserved for those attacks which have an actual march from the periphery of the limb towards its insertion In children the suggestion that a unilateral attack is evidence of local and lateralized permanent change in the cortex should be reserved until some permanent neurological sign develops Ignorance of this peculiarity in children may easily lead to an erroneous diagnosis of intracranial neoplasm and to unjustified and unnecessary intracranial exploration

TREATMENT

Since convulsions are symptoms they should be treated as such When a child who is obviously otherwise well has a spontaneous convulsion it is usually the custom to place him in a hospital for study This is often done specifically to find the cause of his attack In our present ignorance of the pathogenesis of a convulsion such a proce-

ture is really based on a false premise. The result of such study may be the discovery of some specific abnormality which was not at first apparent, but this can only be regarded as a defect in its own right. In a strict sense the cause of the convulsion itself remains a mystery. This is true even in those cases in which such specific defects as inflammation or neoplastic disease of the brain are demonstrated. Not all such defects are associated with convulsions, and further although the defect is constantly present the attacks themselves are only irregular in incidence. If the tumor, or the abscess, or the leptomeningitis is the sole cause of the convulsion the latter should not be irregular in its appearance. Obviously there must be some other chain of events which periodically and irregularly run in specific sequence and which terminate in a seizure. The nature of this chain remains a mystery. Until this is known it is inaccurate to speak even of such a localized abnormality as a hemisphere meningioma as the true cause of localized and lateralized convulsions.

Since this is so, it is even more inaccurate to speak of such things as focal infections, the eruption of the teeth, constipation or fever as the true cause of an attack.

If treatment for convulsions is based solely on an attempt to discover some associated abnormality and if possible to correct it, the convulsions most often will continue to appear after the specific treatment has ceased. It is frequently not realized that even if a patient with a history of localized convulsions has a cortical tumor successfully and completely removed appropriate medical treatment has to be continued for years after the operation before there is a chance of permanent control of the attacks.

Treatment of an Attack.—There is no evidence that the popular remedies of enemas and hot and cold baths so frequently advocated to control a convulsion have any effect in shortening its duration. Certainly in hospital practice they are seldom if ever used. Their only function appears to be to keep anxious and terrified parents safely occupied until the attack comes spontaneously to its close. If, however, a convulsion appears in association with fever it is certainly correct to attempt to reduce the temperature of the child.

A series of convulsions can best be terminated by subcutaneous injection of 1 to 2 grains of *sodium phenobarbital*. This usually requires fifteen to thirty minutes to achieve its effect. This substance in this dosage has a wide tolerance and can safely be repeated even in children less than 1 year old.

Sodium amytal by intravenous injection is difficult to administer or to control in dosage during a seizure and is in no way better in its action than sodium phenobarbital.

Avertin in doses of 50 to 75 mg per kilogram given by rectum is always effective. It is seldom necessary to use, however, except in status epilepticus.

Magnesium sulfate injected intramuscularly in doses of 1 to 2 cc of 50 per cent solution achieves very little and frequently leaves a painful sore Intramuscular injection of 1 to 2 cc of *paraldehyde* is much more effective and without danger

Treatment of Status Epilepticus—A child who dies in status epilepticus does not die from his attacks but from such complications as fever, malnutrition, pneumonia and final cardiac failure For this reason treatment is directed towards the proper administration of food and fluid more directly than towards control of the attacks themselves Since it is impossible to feed a child in status epilepticus by mouth, basal anesthesia should be obtained by *avertin* The initial dose is 75 mg per kilogram of body weight and injections are repeated every four to six hours in doses of 25 to 50 mg per kilo By this system complete muscular relaxation can be maintained with safety, and the child can be fed by gavage In addition, the depth of narcosis is usually sufficient adequately to control the convulsive movements When *avertin* is used for this purpose a small rubber catheter is inserted into the rectum and left in place The end of the catheter is clamped with forceps and the tube is held in place against the inner surface of the thigh with adhesive tape *Avertin* can then be given as it is required and basal narcosis maintained with complete safety for as long as two to three weeks if it is necessary Before the introduction of *avertin* it was not possible smoothly to maintain the necessary degree of narcosis *Paraldehyde* can be used instead but its action is less sure

Prophylactic Treatment Against Future Attacks—*Major Convulsions*—If a child has convulsive attacks associated with an obvious illness it is usual to treat that illness alone and after recovery for all treatment to cease Whether this is wise or not is in any individual case a matter for individual judgment Eight children in ten who have had attacks associated with exanthematous fevers or with such illnesses as leptomeningitis or pneumonia may safely be left without further treatment In the other two cases convulsions will recur spontaneously Since there is no test available which will distinguish the first group from the second it is usual to leave all such children without treatment until such time as convulsions reappear The conservative system is to treat all such children prophylactically for two years with appropriate medicine This in practice is the exception, however, rather than the rule When it is carried out it is based on the assumption that the child who has had an attack with fever has demonstrated that his threshold for cortical inhibition and discharge is lower than the accepted normal It is further assumed that if he is allowed to be without specific treatment until an attack takes place without fever, his threshold for discharge has fallen even lower Then the chance for future prevention of all attacks is even less sure If this program

and of phenobarbital at night time By this system the possible toxic effects of dilantin and the sedative action of phenobarbital are avoided

Since it is usually impossible to predict the onset of an attack the appropriate medicine must be given every day with unfailing accuracy If it is given only after an attack appears it can have no possible action for many hours and can have no action in prophylaxis

Apart from the regular administration of adequate dosage of phenobarbital or dilantin no other type of treatment or maneuver has stood the test of time The Victorian ritual of restricting the life of a person subject to convulsions and the restricting of his diet to an unpleasing and unnatural degree is a mirror of the ideas of righteousness of that period and not of accurate observation A person who has attacks should be allowed in every possible way to live like his fellows. The only difference is that he takes medicine with unfailing regularity

Ketogenic and dehydration diets which had a temporary vogue some fifteen years ago have now almost universally been abandoned Even under the most controlled conditions they achieve success in only one-third of cases and this success is in no way different from that which results from the use of medicine Children who are maintained under strict discipline frequently retaliate to such unpleasant diets by refusing to eat Those with more freedom or greater independence of spirit drink water or eat sugar in secret Despite these severe handicaps of restriction and unpleasantness these two dietary forms of treatment would still be in vogue if they achieved as much as phenobarbital or dilantin

Minor Convulsions—Although minor attacks are less dramatic than major attacks, they are much more difficult completely to control Phenobarbital and dilantin have little effect against them The most useful combination of medicines is that introduced many years ago by Sir William Gowers This is a combination of *sodium bromide and tincture of belladonna* A small dose of arsenic is added to prevent bromide dermatitis The following prescription is an index of what is most useful in a child 10 years old

Sodium bromide	480 grains
Tincture of belladonna	480 minims
Liquor potassii arsenitis	48 minims
Syrup of orange	2 ounces
Water	q.s ad 12 ounces

Dose 2 drams two or three times a day

With this it is usually possible to reduce the number of attacks each day, and frequently to control them completely The chances of complete success, however, are not seven in ten as they are with cryptogenic major convulsions treated with phenobarbital or dilantin

Recently a new substance, *tridione* (3,5,5-trimethylloxazolidine-2,4-dione) (Abbott's), has been introduced which already gives evidence of having a most remarkable success. In children or adults who have minor attacks frequently repeated throughout the day and have no major seizures, tridione will most often produce complete control and maintain it. This result is achieved within a few days. Tridione has apparently little or no action against major attacks. However, a combination of dilantin or phenobarbital and tridione is the most useful prophylactic treatment against major and minor convulsions which has yet been produced.

In all cases where a period of freedom from attacks of not less than two years has been achieved, an added period of not less than six months must be added. During this time the dose of medicine which has been steadily taken is slowly and steadily reduced to zero. If it is interrupted more quickly, the attacks are liable to reappear. This is empirically true, but the explanation for it is unknown.

It is strongly believed by many people that the continuous administration of anticonvulsive drugs produces in its train inevitable mental deterioration. This belief is unfounded. It is due to the confusion of ideas which regards repeated convulsions as a disease and not as a symptom. There are many people who have repeated seizures for many years with no abnormality of their intellectual ability or their emotional balance. There are others, however, who suffer either from defective development of the brain or from slow degenerations of the central nervous system. They have two outward and objective signs of their peculiarity. These are repeated convulsions and mental deterioration. The mental deterioration is frequently ascribed to the repeated convulsions. This is unjustified. Many people falsely ascribe the mental deterioration to the medicine which is taken to control the seizures. This too is unjustified. Phenobarbital and dilantin are used in medicine for other purposes than to control convulsions. With their use under those circumstances the fear of mental deterioration never arises.

Because of a false concept and an unreasoning fear the relatives of a patient who has cryptogenic major or minor convulsions will usually seek continuously to find some other diagnosis. Their usual search is for some theoretical scar or injury in the brain which if found will remove their fear of the diagnosis of "epilepsy." The diagnosis of convulsions associated with cortical scar may be socially more acceptable than that of cryptogenic major or minor convulsions but where such scarring is accurately demonstrated the prognosis for permanent control of the seizures is less good than for those attacks which occur apparently spontaneously.

Once the true pathogenesis of a convulsion is accurately determined it is probable that treatment to prevent its reappearance will be both rapid and sure. Until such time as this is achieved, treatment must

consist of long-continued administration of the optimum dose of a few substances which have demonstrated their efficiency. This is so laborious that many people do not continue it with the necessary faithful regularity. Many of the failures completely to control convulsions are due to this more than to the inefficiency of the medical treatment itself.

NEUROPSYCHIATRIC SYMPTOMS IN ACUTE INFECTIONS OF CHILDHOOD

ABRAHAM LEVINSON, M D *

NEUROPSYCHIATRIC symptoms occurring during acute general infections of childhood should not be minimized. Unfortunately there is a tendency on the part of some physicians to belittle such symptoms particularly when they are transitory in character. Experience has shown that all acute neurologic symptoms are worthy of consideration, for they often complicate the diagnosis and may require special treatment. What is more, they frequently leave their effects on the child long after the original disease has subsided.

CLASSIFICATION

The most significant neuropsychiatric manifestations during infectious diseases are (1) signs of meningeal irritation, (2) convulsions, (3) paresis and paralysis and (4) lethargy, coma and psychosis. Headache, vomiting and abnormally high temperature occur so frequently during acute infections that they are not listed here among the neurologic symptoms requiring special attention, although when they are severe they may be very troublesome.

Meningeal Irritation—As far back as 1894 Dupré noticed that children may have symptoms of meningeal irritation without actual meningitis. Every physician sees children who have a rigid neck, positive Brudzinski, Kernig and Babinski signs with high temperature but who have no meningitis, the cerebrospinal fluid being entirely negative. This condition, spoken of as "meningism" or "meningismus," occurs most frequently at the onset of pneumonia, particularly of the right upper lobe, in otitis media and sometimes also in tonsillitis, bronchitis, pyelitis and severe diarrhea. As a rule the symptoms disappear when the original disease such as the pneumonia or otitis becomes fully developed. The meningeal symptoms, though not very severe, often complicate the clinical picture by masking the original disease and making it necessary to rule out an actual meningitis.

Convulsions—An occasional tremor of the fingers or of the whole hand occurs frequently during acute infections and may not be significant. A convulsion, however, is highly significant. It occurs not infrequently at the onset of pneumonia, tonsillitis, otitis media, pyelitis and diar-

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rhea It is often compared to the chill in the adult. The convulsion may never recur, on the other hand it may be the beginning of an epilepsy, or of an encephalitis. Many cases of epilepsy have their first convulsion during a febrile disease. When the convulsions are transitory or occur only once, the central nervous system of the child may not be affected organically, but there is always a lowered threshold that causes these children to have convulsions. The fact that the majority of children have no convulsion at the onset of an acute infection shows that children subject to them during infection are different from the normal. Unfortunately not only the laity but many physicians consider convulsions during acute infectious disease as of no consequence. This attitude often leads to error in diagnosis and to neglect of treatment.

Paresis and Paralysis—Weakness or paralysis of the muscles of the eyes is quite common. Paralysis of the eye muscles often manifests itself in strabismus or ptosis. It is not always easy to say that the strabismus is due to the infectious disease because of the frequency of strabismus in normal infants and children. Ptosis, however, is more significant, except in the rare instances where there is a history of its presence since birth. Facial asymmetry is not uncommon. It is often difficult to decide between a facial asymmetry and actual facial paralysis. Rigidity of the extremities is also observed. In most cases the rigidity is fleeting in character. If the rigidity persists it is most likely more than a transitory condition. Weakness of one of the extremities is not uncommon. Occasionally there is an actual hemiparesis which lasts for twenty-four hours or longer. The latter gives rise to difficulty in diagnosis.

Lethargy, Coma and Psychosis—Some physicians pay little attention to the mental attitude of the child during acute infections. Close study, however, reveals certain psychologic changes during all acute infections. Some children are listless, others are hyperactive. When these psychologic phenomena are exaggerated, when instead of being listless the child is lethargic or instead of being merely hyperactive he is maniacal, the condition is more than a psychologic attitude.

Lethargy lasting more than a few hours indicates severe disturbances of the central nervous system. Coma is always an alarming symptom. It is particularly important in the differential diagnosis. Maniacal outbursts are very significant. They indicate an acute psychosis, often in a previously psychotic personality. I have seen psychosis in typhoid fever, pneumonia and in as mild a disease as chicken-pox.

DIFFERENTIAL DIAGNOSIS

The presence of neurologic symptoms is easily observed. The difficulty arises in the evaluation of these phenomena. A child is seen at home or at the hospital, the parents give a history of an acute onset,

with headache, vomiting, fever, lethargy and localized or generalized twitchings. Examination discloses rigidity of the neck, positive Brudzinski, Kernig and Babinski signs and perhaps ptosis or paresis of the extremities. What is the significance of these symptoms? What is to be done to arrive at a diagnosis and what is the first step in treatment?

The differential diagnosis lies between an acute infection outside of the central nervous system accompanied by transitory neurologic symptoms, meningitis of all types, brain abscess, brain tumor, epilepsy and in the presence of coma-uremia and diabetes and drug intoxications. The final diagnosis cannot always be made immediately. In most cases it can be made only by a combination of the case history, physical examination and laboratory examination.

History of the Case.—A detailed history, which is important in arriving at any diagnosis, is doubly important in the interpretation of acute neurologic manifestations. A history of acute tonsillitis or general grippal infection speaks for transitory neurologic manifestations. A history of pertussis, measles or German measles, immediately preceding the neurologic symptoms, points to an encephalitis. The presence of an epidemic of poliomyelitis in the vicinity should make one think of that disease, although that may lead to the wrong diagnosis. Every summer many cases of transitory neurologic symptoms are diagnosed as poliomyelitis. A history of tuberculous infection in the patient or tuberculosis in some other member of the family should make one suspect tuberculous meningitis, although tuberculous meningitis has a slow onset, while the neurologic manifestations under consideration have an acute onset.

A history of previous convulsions should put epilepsy in the foreground. A history of chronic nephritis or diabetes would naturally direct attention to uremia or diabetes if the patient is in coma. Administration of large amounts of certain drugs would make one suspect drug intoxication. A history of recent trauma to the head should make one suspect a subdural hematoma or a hemorrhage in the brain proper.

Physical Examination.—A thorough physical examination is even more important for diagnosis than is a detailed history. The discovery of an acute infectious process outside the nervous system such as tonsillitis, otitis media or pneumonia would speak for transitory rather than organic neurologic manifestations, although tonsillitis or pneumonia and meningitis may coexist. The *degree of neck rigidity* sometimes offers a clue to the patient's condition. In most cases of transitory or nonorganic neurologic manifestations, the rigidity of the neck is not very marked while in meningitis it is. This, however, is not always true. I have seen patients with only slight rigidity of the neck suffer from meningitis. *Unilateral* symptoms or signs do not necessarily signify the presence of encephalitis, as some cases of men- particularly of the tuberculous type, are masked by unilat- manifestations. *Absence of reflexes* or weakness of one

partic-
ular
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extremities would speak for acute anterior poliomyelitis, polyradiculitis or polyneuritis. *Exaggerated reflexes* are not of diagnostic significance, as in infants and children the reflexes may be exaggerated even under normal conditions. A positive *Babinski sign* is present in infants under 12 to 15 months of age. A *bulging fontanel* is very suggestive of meningitis. The examination should include a search for *petechiae* on the skin and conjunctiva. If these are found, meningococcal sepsis, commonly spoken of as meningococcemia, is most probable, although other conditions such as subacute bacterial endocarditis and blood dyscrasias may produce petechiae.

The *position* of the patient in bed is suggestive. In most cases of meningitis the patient lies on his side with his knees drawn up while in encephalitis the patient usually lies on his back with his extremities extended.

The *temperature* is of some significance in the diagnosis. In upper respiratory infections the temperature is quite high. In the early stages of tuberculous meningitis the temperature is only moderately elevated. In uremic coma and epilepsy the temperature is usually normal or slightly elevated, although it may be high.

The *pulse*, the clinical indicator which has been so sadly neglected by the modern clinician, may be of some help in the diagnosis. In most forms of meningitis the pulse is very rapid. In brain tumor it is usually slow. In tuberculous meningitis it changes with the stage of the disease, a phenomenon pointed out by Robert Whytt who originally described tuberculous meningitis.

The *respiration* is of some assistance. In acute infections outside of the nervous system, such as pneumonia, tonsillitis and otitis, the respiration is very rapid. In meningitis, encephalitis and poliomyelitis the respiration is not uniform. It may be very rapid, moderately accelerated or even slower than normal. The latter is true in the presence of markedly increased intracranial pressure.

In addition to a thorough physical examination of the chest, abdomen and extremities, attention should be paid to the *ears* and *eyes*. An examination of the ears may disclose an abscess of the middle ear or a mastoiditis which may be the cause of the neurologic manifestations. Examination of the eyes may also give a clue to the diagnosis. Conjunctival petechiae speak for meningococcus sepsis or subacute bacterial endocarditis. Examination of the eyeground may disclose papilledema, choked disk or atrophy of the retina. The presence of choroid tubercles makes tuberculous meningitis a certainty. One does not have to be an otologist or ophthalmologist to be able to examine the ears and eyes. Any practitioner can master the art if he does it often enough.

Laboratory Examination — URINE — Examination of the urine may yield valuable information. Large amounts of albumin point to the neurologic manifestations as uremic in character. Very small amounts of

neurologic symptoms X-ray of the chest and ear may show a pneumonia or mastoiditis Miliary tuberculosis of the lungs shown on x-ray makes the diagnosis of tuberculous meningitis fairly certain X-ray is also helpful in the diagnosis of lead encephalopathy, indicated by the presence of a lead line in the metaphyses of the long bones

CEREBROSPINAL FLUID IN TRANSITORY NEUROLOGIC MANIFESTATIONS

	Normal	Transitory Neurologic Manifestations
Color	Clear, colorless	Clear, colorless
Pressure	Infants and children—40 to 100 mm of water, 3 to 8 mm of mercury	
Cells	1 to 10	Elevated Usually 1 to 10, but may be as high 50
Protein		
Qualitative	Negative	Negative or slightly positive
Quantitative	5 to 48 mg, average 25 mg	Normal or slightly elevated
Sugar	40 to 90 mg	Normal or elevated (to 110)
Chlorides	700 mg	Normal or slightly decreased (to 650)

PATHOGENESIS AND PATHOLOGY

What is the mechanism of the neurologic symptoms occurring during acute infections of childhood and what are the pathologic changes if any? Among the possibilities to be considered are

Edema of the Brain—Edema and hyperemia of the brain are seen frequently in patients who died from diseases other than those of the central nervous system In these cases the edema and the hyperemia of the brain may be responsible for the neurologic symptoms

Serous Meningitis—In some cases there is undoubtedly a serous exudate in the meninges, although it is not always possible to prove this clinically When there is an increase in the amount and pressure of the cerebrospinal fluid and an increase in the cells above the normal 10, and even a slightly positive Pandy test, the patient may have a serous meningitis

Encephalitis—In many patients who die of an acute general infection with neurologic symptoms, there is a petechial hemorrhage grossly and histologically on the external and on the cut surface of the brain In patients who recover there is, of course, no way of ascertaining its presence, which can only be conjectured However, judging by the postencephalitic changes in some of these patients it is fair to assume that at least in some cases there was an encephalitis during the acute infection

Epilepsy—When the convulsion occurring during a general acute infection is followed by repeated periodic attack of convulsions, the first convulsion was undoubtedly due to epilepsy.

Dehydration—Dehydration and the resulting acidosis may be responsible for acute neurologic symptoms in children. This is evidenced by the fact that the neurologic symptoms often disappear as soon as the dehydration is relieved by intravenous fluids.

Low Blood Calcium—In a large series of children with neurologic symptoms during acute infections, I found the blood calcium normal. In a few cases, however, the blood calcium was low. In those cases the low blood calcium may have been responsible for the neurologic symptoms.

Previous Brain Disturbances—It is a common observation that children who have had some neonatal disturbance have convulsions with the slightest infection. It is the old story of the storm hitting the weakest branch of the tree. Children who have shown psychopathic traits during health often become definitely psychotic during an acute infection.

Familial Tendency—Occasionally more than one member of the family has convulsions with every infection. In such cases epilepsy may be the underlying cause. In one instance I discovered the presence of lead intoxication which affected every member of the family. The children had no neurologic symptoms when they were free from infections, but had repeated convulsions as soon as they developed an infection.

Constitutional Basis—Even if no organic basis can be found for the neurologic symptoms, it is likely that children who have neurologic disturbances have some sensitiveness of the brain which is not necessarily epileptic in nature, which in turn makes the brain react to infection. Considering the various possibilities enumerated above one is forced to the conclusion that the pathology and pathogenesis in patients with neurologic symptoms is not uniform. They depend on the cause.

PRECOCIOUS SEXUAL DEVELOPMENT IN CHILDREN

H P G SECKEL, MD *

FOR the purposes of this article it appeared advisable first to discuss some fundamental aspects of normal sexual development in children and then to take up the subject of precocious sexual development. Throughout the paper the terms "sexual development" and "maturation" have been used in preference to the terms "adolescence" and "puberty," as the latter were often applied indiscriminately or seemed to cover overlapping and even opposite sections of the period of sexual development.

NORMAL SEXUAL DEVELOPMENT

Comparative Developmental Study of Man and Animals.—The normal developmental period of man is distinguished from that of other animals by three unique features which put the human being in a class all by himself (Brody, Fig 26) The first feature is the relatively enormous length of the juvenile growth period, i.e., the period from 4 to 14 years of age, the second, the extremely small percentage rate of growth during this period, and the third, the amazingly late appearance of sexual development at the end of this period. Animals, by contrast, have a very short juvenile growth period, grow at a much faster percentage rate and virtually jump from infancy into maturity, lacking almost completely what is known as "childhood" in a human person. In the "postpubertal" period there are no differences any longer between the growth curves of animals and man. These fundamental differences between man and the various animal species can be determined only by dissimilar genetic factors for growth and development.

Maturation of Hypothalamic Centers of Sexual Development—We are all in the habit of accepting without question the well known developmental schedule for certain central nervous functions of the infant, e.g., for his motor performances, speech development, sphincter control and sleeping rhythm. The normal timing of human sexual development at the turn of the first decade and its gradual progress through the second decade appears to be in the same category of a basic fact of human development, tied up genetically with central nervous system maturation. The part of the brain responsible for sexual activity and

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development appears to be in the hypothalamic area of the midbrain (Fig 27, see reviews by Clark et al, Weinberger and Grant) In the mature person some neural or neurohumoral mechanism seems to issue from certain parts of this area which regulate the rate and intensity of impulses passing to the anterior pituitary lobe, thus controlling the output of gonadotropic and other hormones During immaturity this mechanism is evidently inhibited What appears to take away the

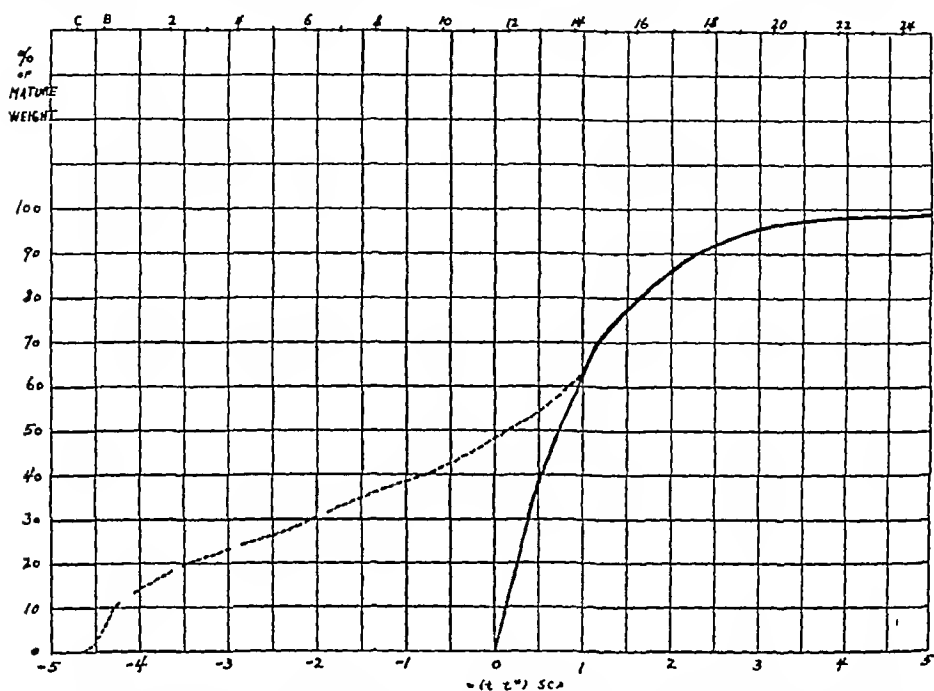


Fig 26—Chart for growth of man (dotted line) and various animals (thin solid line), showing growth equivalence for the phase of growth following "puberty" (thick solid line) To man's age from 11 to 24 years the animals' age from conception to between 8 and 90 months is correlated by mathematical procedure. Animal species studied cow, swine, sheep, pig, rabbit, rat, mouse, cornish fowl, pigeon C= conception, B = birth "The difference between the growth curve of man and that of any other animal under consideration is infinitely greater than the difference between the curves of widely separated species of animals" (After S Brody)

infantile inhibition of the hypothalamopituitary mechanism at the age of normal sexual development is the physiologic maturation of nervous structures in the hypothalamus This normally takes place at the turn of the first and second decades, just as the nervous structures enabling the infant to walk alone normally mature around $1\frac{1}{4}$ years Removal of the depressor effect on the sexual centers may prematurely occur in the immature person through the paralyzing action of a hypothalamic lesion, thus bringing about the "cerebral type" of precocious sexual development, to be discussed later

Development of Production of Sex Hormones.—With a minor reservation (p 203) it can be stated that there is no force in human nature that would promote complete anatomical and hormonal maturation of the gonadal glands other than the pituitary gonadotropic hormones which in turn depend on hypothalamic stimulation. It is only after the onset of maturation of the ovaries and testes that gonadal hormone secretion will induce development of the other primary sex organs and the secondary sexual characteristics. The following survey illustrates the chain of events that leads to hormonal sex maturation

Maturation of hypothalamic sex centers,



Neural or neurohumoral disinhibition of anterior pituitary hormones



Mobilization of gonadotropins (gonad-cell and interstitial-cell stimulating hormones: follicle stimulating and luteinizing hormones in the female, FSH and LH, respectively),



Growth and maturation of gonads (mature follicles, corpora lutea: spermatozoa, interstitial cells of testes),



Mobilization of sex hormones (estrogens, progesterone; androgens)



Maturation of primary sex organs (other than gonads)	Appearance of secondary sex characteristics (for pubic and axillary hair, see Table 2 note 5)
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As is seen in Table 1, small amounts of gonadal sex hormones are excreted in the urine of both sexes during bisexual childhood. Between 11 and 12 years of age, estrogen secretion rises slightly in the boys and very steeply in the girls. In the latter it runs through the well known monthly cycle about one and one-half years before menstruation is established. A cycle is also present later on for pregnandiol, the urinary excretion form of the corpus luteum hormone progesterone (Wooster). The androgens and 17-ketosteroids (mixtures of active and inactive urinary androgens) gradually increase in both sexes, particularly after 11 years of age. According to Talbot and his associates (1943), an oversecretion of androgenic hormones in the male sex is only reached in adult life, while Nathanson and co-workers observed it after 9 years of age. It is thought that the basic excretion of androgenic hormones, as represented by figures for the female sex, is derived from the adrenal cortex, while the surplus in the male sex is excreted by the testicles. Gonadotropic hormone in the form of FSH has been found in the urine of boys not younger than 13 years and of girls not less than 11 years 3 months of age (2.4 to 3.7 rat units per day). That this hormone should be found in the urine later than gonadal sex hormones seems to be due to methodical inadequacy.

Clinical Symptomatology of Sexual Development.—This is roughly outlined in Table 2. A too literal application to individual cases should be

TABLE 1—AVERAGE URINARY OUTPUT PER DAY OF VARIOUS SEX HORMONES BY NORMAL CHILDREN AND ADULTS

Age, Years	Boys				Girls			
	Estrogens IU (a)	Androgens IU (b)	17-Ketosteroids		Estrogens IU (a, c)	Androgens IU (b)	17-Ketosteroids	
			C U (a)	Mg (d)			C U (a)	Mg (d)
3-4	ca 10		40-60	0 15-0 5 (1 0)	ca 10		40-60	0 15-0 5 (1 0)
4-5								
5-6								
6-7	20-25	1-2	60-80	0 65 0 95 1 4 1 9 2 6 3 4 4 3 5 3 6 3 7 2 8 1 11 0	20-25	0 7-3	60-80	0 65 0 95 1 4 1 9 2 6 3 4 4 3 5 3 6 3 7 2 8 1 6 8
7-8								
8-9								
9-10	25-35-60	—	130	90	250(50) 190(80) 380(80)	7	90	0 65 0 95 1 4 1 9 2 6 3 4 4 3 5 3 6 3 7 2 8 1 6 8
10-11								
11-12								
12-13	18-65 (b) 30-95	1-15	185	220	90	7	130	0 65 0 95 1 4 1 9 2 6 3 4 4 3 5 3 6 3 7 2 8 1 6 8
13-14								
14-15								
15-16	10-100 (c)	7-16	215	250	250(50) 190(80) 380(80)	7	160	0 65 0 95 1 4 1 9 2 6 3 4 4 3 5 3 6 3 7 2 8 1 6 8
16-17								
17-18								
Adult		10-110 (55) (e, f, g)			50-300-600 (c, g)	5-10	190	0 65 0 95 1 4 1 9 2 6 3 4 4 3 5 3 6 3 7 2 8 1 6 8

(a) Nathanson et al, (b) Dorfman et al, (c) Oesting and Webster, (d) Talbot et al, (e) Gallagher et al, (f) Dingemans et al, (g) Callow et al
 Estrogens One IU (international unit) = 0.1 microgram (μ g) of estrone, One M U (mouse unit) = 3/5 IU, one R U (rat unit) = 3 IU
 Androgens One IU = 0.1 mg of androsterone, One C U (color unit) = 0.06 mg of androsterone according to Nathanson et al, and = 0.01 mg of androsterone according to Oesting and Webster

avoided as there are wide variations between individuals, families, peoples and races. In girls, especially of Mediterranean and Jewish communities, the earliest signs of breast development and pubic down may be seen at 8 to 9 years, of menarche between 9 and 10 years. In boys the earliest signs of sexual development may be observed around 10 years of age. Up to the age of 10 to 12 years the gonads and other

TABLE 2—AVERAGE APPROXIMATE AGE AND SEQUENCE OF APPEARANCE OF NORMAL SEXUAL CHARACTERISTICS IN BOTH SEXES¹

Age, Years	Boys	Girls
9-10		Growth of bony pelvis.
10-11	First growth of testicles and penis.	Budding of nipples.
11-12	Prostatic activity	Budding of breasts. ²
		Pubic hair. ³
		Vaginal changes. ⁴
12-13	Pubic hair	Growth of external and internal genitalia.
		Pigmentation of nipples.
13-14	Rapid growth of testes and penis.	Mammæ filling in.
	Subareolar node of nipples	Axillary hair. ⁵
14-15	Axillary hair. Down on upper lip.	Menarche ⁶ (average, 13½ years range, 9-10 to 16-17 yrs.)
	Voice change	Earliest normal pregnancies.
15-16	Mature spermatozoa (average 15 years, range, 11½ to 17 years)	Acne. Deepening of voice.
16-17	Facial and body hair	Arrest of skeletal growth.
21	Acne	
	Arrest of skeletal growth.	

¹ Checked with data given by Greulich et al. Jung, Novak (1941), Rosenstern, Schauf fer, Schoenfeld, Shuttieworth, Symposium on Adolescence.

² May start on one side earlier than the other.

³ Consist of change in pH (from 7.2-8.0 to 4.3) appearance of Döderlein bacilli, cornification of vaginal epithelium and deposition of glycogen in it.

⁴ Menstruation may be unovulatory for the first few years.

⁵ Pubic and axillary hair are thought to be due to adrenal-cortical function as stimulated by anterior pituitary corticotropin, (Albright et al. 1942)

primary sex organs hardly grow at all in size whereas thereafter, up to 20 years of age, they achieve 90 per cent of their postnatal growth. The longest diameter of the testicles, for instance, is 1.5 cm. between birth and 11 years and 3.5 cm. at 15 to 16 years. Thus, growth of the "genital type" is greatly lagging behind the "general type" of body growth or the still more advanced "neural" and "lymphoid" types of organ development (Scammon, Holt and McIntosh's "Diseases of Infancy and Childhood," 11th ed., Fig 1, p. 9)

PRECOCIOUS SEXUAL DEVELOPMENT

Etiologic Survey—Two wide apart areas of the human body are functioning as etiologic foci of sex precocity, one in the intracranial cavity and the other on the level of the abdominal cavity. An anatomical specimen of the part of the brain involved, namely, the hypo-



Fig 27—Photograph of median section through the third ventricle of the human brain ($\times 2\frac{1}{2}$) A, Anterior commissure CC, Corpus callosum Ch, Optic chiasm CI, Connexus interthalamicus F, Anterior column of fornix Inf, Infundibulum M, Mammillary body P, Pineal body (From Clark et al, *The Hypothalamus*)

thalamus, is seen in Figure 27. From the third embryonal week this area forms one of three bulbs of the "first brain vesicle," the other two being the cerebral and the optic bulbs. Arising from the rostral end of the intestinal tract, the anterior lobe of the pituitary gland joins up with the anterior hypothalamus of the brain. The embryonal anatomy of the dorsal aspect of the abdominal cavity is presented in Figure 28.

TABLE 3—STATISTICAL SURVEY OF CLINICAL TYPE AND PATHOLOGY OF CASES OF PRECOCIOUS SEXUAL DEVELOPMENT AS REPORTED IN THE LITERATURE

Clinical Type and Pathology	Number of Cases		Authors, Years, Remarks
	Boys	Girls	
INTRACRANIAL, OR HYPOTHALAMIC GROUP			
I <i>Idiopathic Type</i> Without demonstrable pathology (mostly unverified)	89	310	Reuben & Manning, 1922, Bing et al, 1928 ¹ , including 83 cases of precocious pregnancy Cases reported since 1937 ²
II <i>Cerebral Type</i> With demonstrable pathology (verified)	8	11	
(a) Pineal neoplasms	20	1	Bing et al, 1938
	1		Davidoff, 1944
(b) Hypothalamic Pathology (nonpineal)	14	3	Wenberger & Grant, 1941
	8	2	Bing et al, 1938, not listed by Wenberger & Grant.
	1, 1?	3	Cases reported since 1941 ³
		1	Lenz, Case 23 (Wetzler)
ABDOMINAL, OR ENDOCRINE GROUP			
III <i>Endocrine Type</i> (a) Ovarian neoplasms (ver- ified)			Literature to be published by author in survey of Endo- crine Tumors of Infancy Childhood and Adolescence (on file in his office)
(1) Chorionepithelioma		4	
(2) Teratoid tumor		6	
(3) Granulosa cell tu- mors			
Identified ⁴		31	(Literature 1926-1944
Not identified		30	Literature 1825-1933)
(b) Testicular neoplasms (ver- ified)	7		
(c) Adrenal cortical tumors (verified)			
(1) Neoplasms	23	67	See Table 5
(2) Hyperplasias			
Without pseudo- hermaphroditism	5	12	} ⁵
With pseudoher- maphroditism	1?	82	
MISCELLANEOUS GROUP			
Osteodystrophia fibrosa with sex pre- cocity (verified)		26	Sternberg and Joseph (1942)
Others (chiefly unverified)	3	2	See text

¹ Bing's report includes earlier figures of Reuben and Manning's totaling 102 boys and 338 girls, of these, 23 boys and 28 girls with records of "central nervous system involvement" were omitted from this table

² Boys Young (Case 26), Rush et al (2 brothers), Gardiner-Hill (one of twin boys), Bridge, Signist (two brothers), Bronstein (1939)

Girls See Novak (1944), two cases of precocious pregnancy were not included by Reuben and Manning Chaschinsky et al (6 years), Escomel (5 8/12 years)

³ Boy Mindlin et al

Girls Thoms and Hershman, Bronstein (1942), Flicker

Sex not stated (in title) Clément et al, listed as "male?" (publication not available at this time)

⁴ Two cases of the 30 were diagnosed as "follicular cysts"

⁵ These figures are highly approximative and in all probability very incomplete Note that only "verified" cases have been listed

the diagnostic chances are, in the order given, (1) "idiopathic" type, (2) hypothalamic lesion, (3) adrenal-cortical tumor, and (4) testicular neoplasm. The first chance in all likelihood is greater than all others combined. Osteodystrophia fibrosa rarely does occur in boys but is not associated with sex precocity. If a precocious girl without signs of virilization is presented for diagnosis, her chances are, (1) idiopathic type, (2) ovarian neoplasm, (3) Albright's syndrome (if bone disease is present) and (4) hypothalamic lesion. Again, the first chance is greater than a combination of all the others. If virilization is present in the girl, the only diagnostic possibility is adrenal-cortical neoplasm or hyperplasia, pseudohermaphroditism is frequently associated. Arrhenoblastomas of the ovary with virilization and defeminization were described only after sexual maturation, in girls no less than 15 years of age.

General Clinical Picture of Sexual Precocity—Sexual development should be called "precocious" only if symptoms of sexual maturation make their appearance below 10 years of age in boys and below 8 years in girls. The old and somewhat clumsy term "macrogenitosomia" suggests that besides genital precocity there is also somatic precocity. The latter consists of a premature growth spurt that makes a giant of the child among his playmates. The bone age is more or less correspondingly advanced. The same is not always true of the tooth age, baby teeth may appear prematurely but the second dentition is usually slow and out of proportion with the bone age. The facial appearance is frequently childlike. Naturally, all other organs take part in the macrosomia, particularly the muscle system ("infant Hercules"). According to intelligence and personality studies, including psychosexual behavior, cerebral development is infrequently advanced beyond chronological age, not seldom even retarded. This complete dissociation, in varying degrees, between chronological age, bone age, tooth age, sexual age and mental age of the child is highly characteristic of the syndrome under discussion.

Genital precocity might be described in terms of a variety of clinical forms. It is either "complete" or "incomplete," according to whether or not the gonadal glands are included in the process of precocious maturation. "Complete" sexual precocity in this sense is observed almost exclusively in the hypothalamic group of cases, i.e., the idiopathic and cerebral types. This form has also been called "true precocious puberty" and is always of the so-called "isosexual (homologous)" variety, following the true sex of the patient in its clinical pattern. "Incomplete" sexual precocity, on the other hand, is prevalent in the endocrine type of the disorder, follows either the isosexual or the "heterosexual (heterologous)" clinical pattern and has also been described as "artificial" or pseudo-precocious puberty. In both forms the sequence and speed of appearance of sexual characteristics approximate those of normal sexual development (Table 2). How-

TABLE 4—DIFFERENTIAL DIAGNOSTIC DATA CONCERNING THE VARIOUS TYPES OF PRECOCIOUS SEXUAL DEVELOPMENT

Clinical, Pathological and Hormonal Data	Intracranial Hypothalamic Group		Abdominal Hormonal Group			
	Idiopathic Type Boys, Girls	Cerebral Type Boys Girls	Endocrine Type			
			Granulosa Cell Tumor of Ovary	Interstitial Cell Adenoma of Testicle	Boys	Girls
Gigantism, advanced bone age	Definite	Definite	Moderate ²	Definite	Definite to moderate	Definite to moderate
Clinical form of sex precocity	Isosexual, complete	Isosexual, complete	Isosexual, incomplete	Isosexual incomplete	Usually isosexual in-complete	Usually heterosexual, in-complete
Gonads	Mature Present	Mature Present	Infantile	Infantile Absent	Usually infantile	Usually complete
Spermatozoa	Ovulatory (Premenstrual secretory phase) ¹	Ovulatory (Premenstrual secretory phase) ¹	Unovulatory	—	Usually absent	Usually infantile
Menstruation	Present	Present	Proliferative phase Absent	—	—	Usually absent
Endometrium	Present	Present	Absent	—	—	Not recorded
Ovulation	Present	Present	Absent	—	—	Absent
Corpora lutea	Present	Present	Rather good	Absent Good	—	Absent
Fertility	Good	Serious	Usually increased beyond normal women's range	Not recorded	Depd on Type of Tumor and Sex + + +	Absent
Prognosis	Not recorded	Increased for chronological age but within normal adult range of same sex	Not recorded	Not recorded	Increased within or beyond normal men's range	Neg or increased beyond normal women's range
Ur (urinary) estrogens	Increased for chronological age but within normal adult range of same sex (boys only)	Same as in Idiopathic Type (both sexes)	Not recorded	Not recorded	Increased within or beyond normal men's range	Increased within or beyond normal men's range
Ur androgens	Not recorded	Not recorded	Not recorded	Not recorded	Neg or small amounts Negative	Negative or elevated Negative
Ur 17 ketosteroids	Negative ³	Negative ³	Usually negative	Negative		
Ur pregnandiol						
Ur gonadotropin						

¹Not yet observed but likely to be found²See, Talbot and Talbot, *Loc. cit.*, Table I, p. 35³Probably due to methodical inadequacy

ever, in the complete form it includes more or less advanced maturation of the gonads while in the incomplete form it stops short of it. In the latter situation the clinician is confronted with what Apert has described as "dissociated virilization," or feminization, of boys and girls, respectively, consisting of a striking discrepancy between small and immature testicles, or ovaries, and fully developed nongonadal primary sex organs (penis, prostate, seminal vesicles, vulva, vagina, uterus, tubes) This phenomenon is of great diagnostic importance for discerning clinically between the hypothalamic and endocrine groups of sexual precocity Heterosexual sex precocity is always "incomplete" and practically confined to girls with adrenal-cortical pathology, showing virilization with either normal or congenitally malformed nongonadal sex organs (pseudohermaphrodites)

A summary of the criteria of "completeness" or "incompleteness" of precocious sexual development is as follows (1) presence, or absence, of anatomical maturation as to size and microscopic structure of ovaries and testicles, (2) presence or absence of mature spermatozoa and mature graafian follicles, ready earlier or later for emission and rupture, respectively, (3) presence or absence in girls of ovulatory menstruations, i.e., cyclic bleedings associated (possibly months or years after menarche) with ovulation, formation of corpora lutea and the secretory phase of endometrium, (4) occurrence or nonoccurrence of precocious fertilization (precocious pregnancy in girls), (5) urinary excretion of gonadal sex hormones, in the complete form, in amounts somewhat less than, or equal to, those excreted by normal adults of the same sex, in the incomplete forms, in amounts usually far exceeding the range of normal adults of the same or even the opposite sex (adrenal-cortical androgens included, Table 4)

Pathology and Clinical Consideration of Special Types.—In this section complementary remarks will be made on the pathology, pathogenesis, clinical findings, laboratory tests and management of the three main types of precocious sexual development.

IDIOPATHIC TYPE OF SEXUAL PRECOCITY

There are no demonstrable intracranial, abdominal or other lesions found in these cases. There is one negative autopsy on record (Lenz' Table, Case 80) and on occasional laparotomies tumors of the ovaries and adrenals were missing (Novak) Most of these people live through a normal life span which seems to be incompatible with intracranial or abdominal pathology Individuals in this group, by some freak of nature, achieve maturation of their hypothalamic sex centers at an unusually early age "appearing to skip all or part of their childhood and at times jumping from infancy to puberty" (Novak) This reminds one of the type of growth and development of various animal species, i.e., of an atavistic mechanism (Fig 26) Somehow, the genic factor,

or factors, that determine the time of hypothalamic sex maturation must be at fault. This concept is confirmed by records of a small percentage of heredofamilial sexual precocity in this group (Stone, Lenz, Reuben and Manning, Bodd, Bauer, Orel, Sigrist, Rush et al, Fig 29). One of unidentical twins was reported to show the syndrome (Gardiner-Hill).

In boys of this group, attainment of complete precocious sexual maturation with adult testicular size and function has been sufficiently emphasized above (lit Table 3, Note 2, Stone). Owing perhaps to the

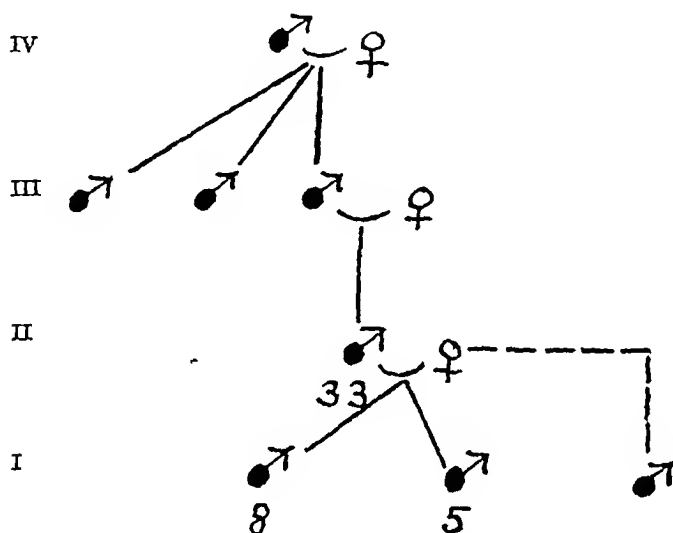


Fig 29—Idiopathic type of precocious sexual development in male members of four generations (drawn after Rush et al). Age at sexual maturation in fourth and third generations not stated. In the second generation, father, now 33 years of age, started sexual development at age of 5. Of his two sons, the 8 year old one is sexually developing since the age of 18 months (now, 66.5 in., 88 lbs, bone age of 17 years), the 5 year old one since the age of 3 years (now, 49.5 in., 51 lbs, bone age of 12 years). There is a distant cousin on the mother's ('1') side with the same syndrome. Father and two sons showed negative tests for urinary prolactin, "positive" tests for urinary male sex hormone.

♀ Normal females

♂ Precocious males

usual lack of psychosexual aggressiveness of the boys, precocious fertilization seems extremely rare (one case cited by Stone, one by Klaus, 7 and 9 yrs). As a rule procreation occurs at the ordinary age.

In girls, precocious maturation of ovarian size and function is practically impossible to demonstrate by clinical examination. Regular menstruation is no proof of ovulation, since unovulatory estrogen-induced menstruation does occur in healthy girls early after menarche and in girls with estrogen-producing tumors of the ovaries or, rarely, the adrenal cortices. Proof of actual ovulation can be furnished only

indirectly by demonstrating the progesterone-induced secretory phase of the premenstrual endometrium which is a sign of corpus luteum function. Such endometrial biopsy has apparently never been taken in a girl with idiopathic sexual precocity, it is expected to be positive, at least some time after onset of menstruation. Direct autoptic information on the ovaries is only slightly less scanty in this group of girls than are clinical studies. In Lenz' necropsy of a girl, aged 3 years, no contributory findings other than evidence of long lasting ovulation and presence of a corpus luteum were reported. Corpora lutea were excised on laparotomy in four girls with idiopathic sexual precocity (Keatinge, Case 2, Novak, 1944, three cases, Fig 30)



Fig 30—Photomicrograph of youngest corpus luteum on record. Girl, aged 22 months, with idiopathic sexual precocity (Novak, 1944 Case 1) (Am Jour of Obst. & Gynec., Vol. 47 C. V. Mosby Co.)

The final proof of ovarian maturity in a prematurely developed girl is brought forth by the presence of precocious pregnancy. The relative frequency of this event may be due to the psychosexual defenselessness of the precocious girl. Eighty-three such cases out of a total of 310 cases of female precocity were collected by Reuben and Manning (26.6 per cent, Table 3). Sixty-eight of the pregnant girls were between 11 and 14 years at the time of delivery, the majority of them had had signs of precocious puberty prior to pregnancy. Sixteen girls were between 6 and 10 years at the time of delivery. To this youngest group of mothers two more recent cases can be added (Chaschinsky, 6 years, Escomel, 5 years 8 months, Fig 31). In Escomel's girl, menarche occurred at 3 years, breasts and pubic hair were developed at

4 years and conception took place at 5 years $\frac{1}{2}$ month, a boy of 2700 gm was delivered by cesarean section and an ovarian biopsy showed adult type of tissue and the corpus luteum of pregnancy Bodd's case was unique inasmuch as the infant born to the 8 year old mother showed pubic and axillary hair at birth Barbier mentioned a grandmother of 22

The outlook for the future seems favorable in children with idiopathic sexual precocity Owing to premature closure of the epiphyseal lines of the long bones, they grow up to be understatured adults Their dentition, mental development and psychosexual maturation gradually catch up with their premature macrogenitosomia In at least three-



Fig 31—"The world's most youthful mother" (Escamel, 1939) Precocious pregnancy in a girl delivered of a son at 5 years 8 months of age

fourths of the cases they will marry at the customary time, have healthy children and die at various ages of ordinary causes (see Fig 29) Five such life stories of women are listed in Lenz' table (Nos 12, 28, 29, 63, 89), two of them menstruated from 2 to 52 years or over, one died at 75 A not insignificant percentage of the female cases will have their first child between 5 $\frac{1}{2}$ and 14 years of age Precocious senility seems to be most unusual

Laboratory procedures such as x-rays of the skull and urinary structures give negative results in this group Urinary sex hormone excretions were never studied in girls and only four times in boys (Rush, Fig 29, Bronstein, 1939, 9 $\frac{1}{2}$ years, excess prolactin, androgens 55 I U per liter, Gardiner-Hill, 8 $\frac{3}{4}$ years, 17-ketosteroids normal for

chronological age, Bridge et al, 5 years, 17-ketosteroids on level of 12 to 16 year old boys, see Table 4)

The management of a boy with idiopathic sex precocity should include repeated examinations for intracranial disease, adrenal cortical tumor and neoplasm of a descended or undescended testicle. Psychological management is the same as for girls (*vi*). In girls, repeated pelvic and neurological explorations are imperative and premenstrual endometrial biopsies and urinary pregnandiol excretion studies may contribute much to a proper diagnosis. Exploratory laparotomy may be dispensed with "if careful pelvic examination under anesthesia reveals no suggestion of ovarian enlargement or tumor" (Novak, 1944). If, however, a genuine suspicion of ovarian tumor remains, a laparotomy seems warranted (Sevringhaus). Psychological management consists of avoiding the development in the girl's and her mother's mind of a high degree of disease-consciousness and sense of inferiority. The mother should be informed of the favorable prognosis and all steps should be taken to protect the girl from sex violation and precocious impregnation.

CEREBRAL TYPE OF SEXUAL PRECOCITY

Intracranial pathologic processes are demonstrable in these cases either in the pineal gland (teratoma, chorionepithelioma, pinealoma) or extrapineally. In the latter case, the lesions are found in or near the hypothalamus and consist of hydrocephalus, cysts, congenital anomalies, tuberous sclerosis, various neoplasms and encephalitis (chronic bacterial meningo-encephalitis, epidemic influenza and measles encephalitis, see Weinberg's and Bing's tables, Table 3).

Among the much discussed pineal neoplasms, fifty-six out of a total of 177 cases on record occurred below 15 years of age, of the fifty-six, only twenty-one, or 37.5 per cent, showed the clinical picture of sexual precocity (Bing et al.). In the twenty-one cases, destruction was invariably found in the hypothalamus and 70 per cent of them were associated with hypothalamic disorders other than sex precocity such as polydipsia, polyuria, polyphagia, obesity, sleep disturbances and nonfebrile changes in temperature and pulse rate. In the remaining two thirds of cases of pineal neoplasms in patients below the age of 15, this hypothalamic syndrome including sexual precocity was missing and the tumors failed to interfere with the hypothalamic region. If such statistical, pathologic and clinical studies are taken together with the still ambiguous experimental data concerning a supposed hormonal function of the pineal body (Rowntree, others), the conclusion seems inevitable that pineal neoplasms with sex precocity belong in the group of hypothalamic pathology (Bing et al.) rather than that of endocrine tumors (Davidoff). A confirmation of this assumption comes from the study of extrapineal hypothalamic lesions

causing sexual precocity which in some instances "were so small and so restricted to the mammillary bodies that they may almost be compared to experimental lesions" (Weinberger-Grant) They are also found near the tuber cinereum, infundibulum, optic chiasm or, more often, in the posterior hypothalamus In such cases the same hypothalamic syndrome as described in pineal tumors intruding upon the hypothalamic area has been found to accompany sexual precocity

It should be noted that neoplasms of the anterior pituitary do not appear in the pathologic survey When such adenomas were found in immature children, either no clinical symptoms or those of Cushing's syndrome were present, but there were no indications of sexual precocity On the other hand, in the latter condition no pituitary neoplasm has ever been demonstrated (Only possible exception Albright's disease of girls, p 206)

The clinical studies referred to seem to indicate that precocious sexual development of the cerebral type is a hypothalamopituitary disorder Lesions in or near the hypothalamus "destroy some portion of the mechanism or neural pathways which normally serve to control or inhibit the rate, character or intensity of the nerve impulses passing to the pars distalis" (Weinberger-Grant) Once the anterior pituitary is disinhibited by the local lesion, the entire chain of hormonal events which leads to complete isosexual precocity is set in motion (p 185) Why, in contrast to the sex distribution in the idiopathic type, many more boys than girls are found in the cerebral type (44 9), especially in cases with pineal tumor (21 1), is impossible to explain at the present time

It is not proposed to go into details of neurological diagnosis of pineal and hypothalamic lesions If a boy presents himself with the obvious picture of isosexual precocity who at the same time has a bad squint, Argyll-Robertson pupils or an inability to turn his eyes upward, everybody will put his case in the pineal section of the cerebral type It should be noted, however, that things are not always as simple as this and that a great variety of symptoms of upper cranial nerve involvement, increased intracranial pressure and hypothalamic disorder may be encountered in such patients (Bailey, Buchanan, Bucy, Bing et al, Gross, Weinberger-Grant) Furthermore, no neurological findings other than sex precocity may be found for some time in a child with a slow growing lesion of the hypothalamus, especially in or near the mammillary bodies Thus, a case with an asymptomatic lesion may initially be misclassified as "idiopathic" sexual precocity

The clinical picture of the cerebral type of sexual precocity is isosexual and complete in both sexes which implies maturation of the testicles and ovaries (Table 4) In the boys with verified pineal tumors listed in Bing's table 2 description of the testes is often inexact ("enlarged" or "adult genitalia"), but in two cases spermatogenesis was reported to be present and in another case the testes were said to be

well developed In necropsies of extrapineal hypothalamic tumors of eleven boys listed in Weinberger's table, the testicles showed either increased weight or overgrowth of interstitial tissue or active spermatogenesis In Mindlin's patient the testicles were described as adult size In the nine cases concerning girls (Table 3), postmortem studies of the ovaries were made in four They revealed hyperplasia with microscopic degeneration in Dorff-Shapiro's case, mature graafian follicles in Gross' case 7, mature follicles and a corpus luteum in the case of Clark and his co-workers, and adult ovaries in Lenz' case (8 years old, hydrocephalus, monstrous obesity) Gross also described hyperplasia of endometrial glands and cornification of vaginal epithelium in his case Fertilization has never been reported in either sex in the cerebral type of sexual precocity

As to laboratory procedures, radiologic examinations of the skull with and without air filling may reveal internal hydrocephalus, displacement of structures and midline calcifications in the pineal area, or elsewhere Urinary sex hormone excretion has been studied in four verified instances In one, a boy of 10 with pineal tumor, Horrax found a large excretion of androgens (no exact data) The other three cases belong in the extrapineal hypothalamic group In a boy almost 8 years old, Weinberger and Grant reported negative gonadotropins but 10 to 45 LU of androgen in three daily specimens (normal adult male range) Gross, studying a 26 month old girl having symptoms for seven months, found no gonadotropins but 12 to 648 (average 267) mouse units of estrogens in seven daily specimens, which is equal to an average of 160 IU (normal adult female range) Tests for estrogens, pregnandiol and gonadotropins were negative in a 22 month old girl reported by Bronstein and associates (1942), she had had symptoms for only one month

The prognosis of the cerebral type of sexual precocity is much more serious than that of the idiopathic type This is evidenced by the many necropsy reports in the tables referred to An intracranial tumor is liable to cause trouble within one or two years, and survival without intracranial signs for periods longer than that puts a case of complete isosexual precocity automatically into the idiopathic type

Management of these patients is largely a problem of neurosurgery or/and roentgen therapy Few children so far have survived attempts at treatment for any length of time (Flicker, four year survival, Weinberger-Grant two and one-half months postoperative observation) Psychological guidance should be roughly the same as in the preceding type, but the greater seriousness of the outlook and the lesser dangers of precocious fertilization must be taken into consideration

ENDOCRINE TYPE OF SEXUAL PRECOCITY

Endocrine Tumors of the Ovary—*Teratoid Embryomas and Chorion-epitheliomas*—The former of these ovarian neoplasms give rise to

endocrine sexual precocity only very exceptionally and do resemble the granulosa cell tumors clinically and hormonally (see below). The ovarian chorionepithelioma of the virginal child (6 to 8 years, four cases) is an extremely rare cause of sexual precocity. It inevitably leads to death with metastases within one and one-half years. The outstanding clinical feature is the contrast between the cachexia and the exuberance of precocious sexual maturity. The latter, in contrast to the great majority of cases of adrenal cortical precocity in girls, is clearly isosexual in character. Menstruation is probably unovulatory, for the contralateral ovary of one patient was of adult size and contained numerous follicular cysts, there were no mature graafian follicles and no corpus luteum. The ovarian changes are probably due to the action of chorionic hormone which was demonstrated in the tumor tissue of one case and the urine of three cases. Urinary estrogens were greatly increased in one case (600 IU per day). Chorionic hormone and estrogens disappeared temporarily after operative removal of the ovarian tumor, the former hormone reappeared with the subsequent spread of metastases.

Granulosa Cell Tumors—In the thirty-one "identified" instances collected in Table 3, onset of sexual precocity was observed at 5 months to 7½ years of age. Four more cases with menstrual irregularities occurring between 11½ and 14 years of age were not included. In thirty "unidentified" instances from the older literature, association of precocity with an ovarian "sarcoma" was verified by either operation or necropsy, and fourteen times regression of signs of sex maturation was recorded to have followed the removal of the tumor. Granulosa cell tumors of immature age form about 10 per cent of the total of all age groups. From a clinical point of view they appear to be predominantly benign adenomas when seen in the first decade. Of the thirty-one patients only two have died with metastases and less than half of the remaining tumors showed low grade microscopic malignancy. Twenty-nine girls survived removal of the tumor from one to ten years.

The clinical picture presented by these girls was that of incomplete isosexual precocity. Body growth, skeletal age and development of nongonadal primary and secondary sex organs were greatly, not seldom fully, advanced. In one of the ovaries, occasionally later in the other, too, a tumor the size four times a normal infantile ovary up to a man's head was palpable on pelvic or abdominal examination. The normal ovarian rest on the side of the tumor and the contralateral ovary were completely infantile, with neither maturing follicles nor signs of ovulation nor corpora lutea. Unovulatory vaginal bleedings were missing only once and appeared for the first time after removal of the tumor in two cases ("estrogen withdrawal bleeding"). In less than half the cases regular menstrual periods were established, sometimes menorrhagic in degree, single vaginal bleedings or irregular

metrorrhagias were seen preoperatively in the remaining cases. The endometrium showed glandular hyperplasia of the interval stage in three observations. Precocious pregnancy has never been reported. Psychosexual maturation was occasionally seen.

Management of these patients consists of ovary-salpingectomy with removal of the tumor. Local recurrences are not on record. Post-operative regression of sexual precocity towards the infantile state is the more complete the younger the girl at the time of operation, there will be little or no regression following an operation done at the age of 8 years or over. Normal sex development with ovarian maturation will make its appearance at the physiological age. Due to premature development of bony epiphyses, growth will be stunted to a certain extent.

Granulosa cell tumors in this group of girls were shown to contain large amounts of estrogenic hormones (eight cases). Urinary estrogens were demonstrated in eight cases, three of them showed 10,440, 3,000 and 17,500 IU respectively per liter, but one only 5 IU per liter. Three cases gave a weakly positive Aschheim-Zondek reaction, six a negative one. After removal of the ovarian tumor estrogens disappeared from the urine in a short time, they recurred after appearance of an identical tumor in the other ovary in two cases. Thus, an excessive and uncontrolled estrogen excretion on the part of the ovarian tumor appears to account for the clinical syndrome (Table 4).

Endocrine Tumors of the Testicles.—There are two chief varieties of such tumors, teratoid embryoma and interstitial cell adenoma. An unidentified bilateral tumor of the first variety causing sexual precocity at 3 years of age is on record in the old literature. Later on, six cases of endocrine interstitial cell adenomas of one testicle were reported in boys aged 3 to 6 years at the onset of sexual maturation. All but one were identified microscopically. The comparatively high age at the onset of tumor growth and the absolute benignity of these tumors is very much in contrast to the great malignancy and low age of onset (62 per cent under 3 years) of all sorts of nonendocrine testicular tumors of childhood including teratomas.

The clinical picture is that of incomplete isosexual precocity associated with a unilateral testicular tumor (Table 4). The size of the tumors varied from 1.2 to 10 or 12 cm for the longest diameter. The contralateral testis was completely infantile ("dissociated virilization"). Seminal ejaculations and fertilization were not reported. In one case the normal tissue of the tumorous testicle showed premature development of seminiferous tubules and various stages of sperm cell development, but no mature spermatozoa. Gynecomastia was present in one case. Tumor or urinary androgens were never examined and the Friedman test was negative in three cases. After removal of the tumor a more or less striking regression of sexual characteristics took place in three cases in the course of several months. In three boys,

aged 6, 9 and 11 years at the time of operation, no change in the clinical picture was seen after one and one-half to two years. Increase in size of the remaining testicle three to nine months after operation was reported in two boys aged 7 and 10½ years, respectively. This could be interpreted as compensatory hypertrophy of the testicle in the first instance and as testicular growth spurt of normal sex development in the second instance. Since these tumors are benign, there is no reason to hasten orchidectomy and omit pre-operative hormone studies.

TABLE 5—CLASSIFICATION OF CLINICAL TYPES OF ADRENAL-CORTICAL SYNDROME IN TWENTY-SIX BOYS AND SEVENTY-EIGHT GIRLS SHOWING SYMPTOMS FROM VERIFIED FUNCTIONAL ADENOMA OR CARCINOMA OF THE ADRENAL CORTEX BELOW AGE OF 15 YEARS

BOYS, 26 CASES

A <i>Precocious Virilization (Isosexual Precocity)</i> (23 Cases)	
I Plain virilism without gigantism but occasional obesity	8
II Virilism with gigantism but no obesity (Infant Hercules)	9
III Virilism with Cushing's syndrome	6
B <i>No Sexual Precocity</i> (3 Cases)	
I Cushing's syndrome with typical obesity (age 4½ months)	1
II Cushing's syndrome with sexual infantilism (age 14-17 years)	1
III Feminization at normal maturity (age 14-15 years)	1

GIRLS, 78 CASES

A <i>Precocious Virilization (Heterosexual Precocity)</i> (60 Cases)	
I. Plain virilism with and without gigantism or obesity	25
II. Virilism with gigantism but no obesity (Infant Hercules)	9
III Virilism with Cushing's syndrome	17
IV Mixed virilization and feminization	9
B <i>Precocious Feminization (No Virilism, Isosexual Precocity)</i>	7
C <i>No Sexual Precocity</i> (9 Cases)	
I Obesity of Buffalo type, no virilism	2
II Virilism with Cushing's syndrome but normal sexual maturation (aged 11 years)	1
III Virilism with Cushing's syndrome and secondary or primary amenorrhea around age of normal sex development	6
D <i>Unclassifiable</i>	2

Note A complete tabulation and bibliography of the patients listed in this table is on file in the writer's office

Endocrine Tumors of the Adrenal Cortex—These tumors are either true neoplasms, adenomas or carcinomas (erroneously called "hypernephromas"), or bilateral hyperplasias (Table 3, 5). Of the cases listed in Table 5, about 70 per cent were carcinomas and 30 per cent adenomas, one tumor arose ectopically in an ovary. The weight of the neoplasms varied from 12 gm to 6 to 7 kg. In about two thirds of the carcinomas there were metastases to the liver, lungs, veins and lymphatics. There was no consistent correlation between the diverse histologic forms of the tumors and the clinical pictures or hormone findings of the patients.

The so-called "adrenocortical syndrome" as caused by adenoma or carcinoma of the adrenal cortex is reviewed in Table 5. Seventy-five per cent of the patients were below 8 years of age. The predominant clinical type was precocious virilization, the so-called "adrenogenital syndrome," isosexual in character in the boys, heterosexual in the girls. The virilism consisted of an enlarged penis or clitoris, growth of sexual and body hair, herculean musculature, deep voice and facial acne. It was variously associated with gigantism, advanced bone age, obesity, hypertension, Cushing's syndrome, and partial feminization. In the latter case, the virilized girls showed precocious breast development, or vaginal bleeding, or both. An instance of gynecomastia was recorded in a boy of 14 to 15 years. He belongs in the group "No sexual precocity" (Table 5), as do the patients with primary or secondary amenorrhea, Cushing's syndrome, sexual infantilism, and so forth. An upper abdominal tumor is often palpable or found on intravenous pyelography. General cachexia is not infrequently seen and Addison's syndrome may develop in the late stages.

Simple hyperplasia of the adrenal cortices, or aberrant cortical tissue in the ovary (Saphir-Parker) or testis (Wilkins et al.), is frequently associated with precocious sex development of the virilizing type. While the cortical hyperplasia is congenital in nature, the clinical picture of precocious virilization may develop at any time between birth and ten years. If it appears at a later age, it is no longer considered "precocious." In a minority of the precocious cases the external genitalia are normally built, according to the gonadal sex, with the exception of enlargement of the penis or clitoris (Table 3, Cases "without pseudohermaphroditism"). The majority of cases with precocious virilization presents congenital malformations of the genitourinary tract such as hypospadias, other urethral abnormalities and absence of vagina or vulva (Table 3, Cases "with pseudohermaphroditism"), the gonads are much more frequently female than male. It has been suggested that in cases of female pseudohermaphroditism the developmental anatomy of the embryo's genitourinary tract has been masculinized by the presence of hyperplastic, hormonally overactive adrenal cortices.

The "incompleteness" of adrenal-cortical sex precocity was evidenced in the boys by the presence of "dissociated virilization" (Table 4). In contrast to a herculean, hairy, fully masculinized body, the testicles remained infantile in size, with no microscopic signs of spermatogenesis. From this rule there were only two exceptions in 5 year old boys, one with adrenal-cortical carcinoma, the other with adenoma, in both cases the testes were enlarged, once to adult size, and mature spermatozoa were demonstrated. Similarly, in the girls the ovaries ordinarily appeared of normal size for age, or full of follicular cysts, or outright atrophic. "Enlarged" ovaries were recorded with comment in four cases and graafian follicles in two girls aged

years Corpora lutea or remnants of such were only seen in adolescent virilism (Group C, Table 5) The majority of children of this type were psychosexually immature Fertilization has never been recorded

As to hormone studies, malignant tumor tissue was assayed for androgens with positive results in two girls Urinary Aschheim-Zondek or Friedman reactions were consistently negative in all three types of cortical tumors Urinary androgens were excreted in excessive, i.e. more than normal adult male quantities in the majority of boys and girls tested in this series who had cortical adenoma or carcinoma (ten cases, Table 4) For "androgens" the range was from 160 to 1120 IU per day, for "17-ketosteroids" from 27 to 288 mg per day Lower figures but still too high for chronological age were found in a boy and a girl, aged $1\frac{1}{2}$ years (3 to 62 mg per day 17-ketosteroids) Among the verified cortical hyperplasias urinary 17-ketosteroids varied from 7.8 to 22.4 mg per day in eight cases and went as high as 29 to 176 mg per day in five cases, in Wilkins' boy of $3\frac{1}{2}$ with associated Addison's syndrome 30 IU per day of androgens were found If total, or neutral, 17-ketosteroids were analyzed for beta-alcoholic and non-alcoholic fractions, the latter were found to be unusually high in patients with cortical carcinoma and very low in verified hyperplasia (two and seven years, respectively, Talbot et al⁶³) Urinary estrogens were excreted in normal amounts for chronological age in five girls with adrenal-cortical neoplasm In two other girls they appeared in excessive amounts (e.g., 540 to 10,120 IU per day at $3\frac{1}{2}$ years, Gross, Case 2), androgens were excreted in excess at the same time and there were no feminine characteristics Urinary pregnandiol was "elevated" in one and negative in another girl with cortical adenoma, in eight cases of verified cortical hyperplasias three boys and four girls ranged from 0 to 3.3 mg per day and one girl excreted 36 mg per day (Talbot et al⁶³, Genitis-Bronstein)

In a certain number of children urinary hormone excretions returned to normal chronological age levels following operative removal of cortical neoplasms, along with clinical regression of virilizing and other hormonal effects on the body If and when metastases arose postoperatively, excessive urinary androgen levels returned early (Friedgood-Gargill) In successfully operated children normal sex development will take place later at the proper age via the hypothalamo-pituitary mechanism In the same manner, completion of sexual maturation, especially gonadal, will be seen in precociously virilized boys with cortical hyperplasia (Fig 32) In girls with virilizing cortical hyperplasia no spontaneous isosexual maturation may be expected (see reviews by Kepler-Keating, Kenyon, Cahill)

The treatment of choice for children with adrenal-cortical carcinoma is prompt operative removal of the tumor followed by proper radiation therapy Diagnostic procedures such as x-ray studies of skull, lungs and bones, intravenous pyelogram, air insufflation x-ray

of the kidney area (cave!), blood chemistry and urinary hormone studies are not to take longer than a few days. Postoperative prevention of cortical insufficiency, caused by relative or absolute lack of proper secretion on the part of the contralateral adrenal, is a matter

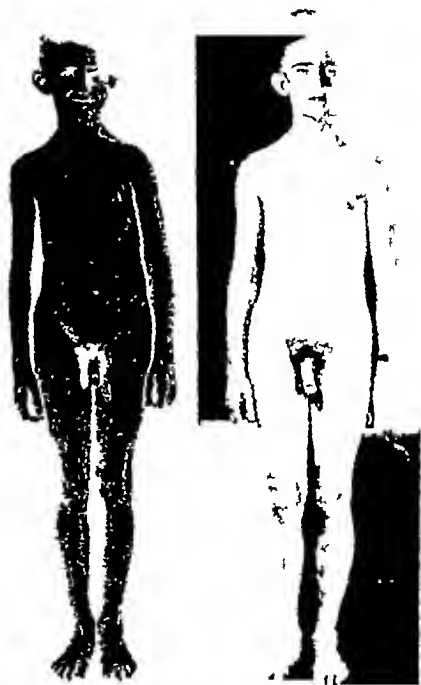


Fig. 32.—Adrenal cortical virilism due to hyperplasia of the adrenal cortex (Talbot Butler Berman, *J. Clin. Investigation*, Vol. 21) Left. Patient at $7\frac{1}{2}$ years, shortly before unilateral adrenalectomy Right. Patient at $11\frac{1}{2}$ years. Note increase in size of testes.

of great concern. In cortical adenoma surgical treatment is the same, but the outlook appears much better. In cortical hyperplasia unilateral removal or partial resection of adrenal cortex has proved unsatisfactory in girls and unnecessary in boys. If the diagnosis is questionable, exploratory laparotomy may seem indicated. Anatomical malforma-

tions of the genitalia require surgical correction. In girls, orally administered diethylstilbestrol will promote development of female sex characteristics. This is also part of the psychological management which deserves great attention in either sex.

MISCELLANEOUS GROUP

A few short references may suffice to direct the reader's attention to some odd conditions falling under this heading. (1) Osteodystrophia fibrosa in girls (Albright's disease, 1937) consisting of bone disease, skin pigmentations, complete (?) isosexual sex precocity and inconstant exophthalmic goiter. In boys sexual precocity is missing in the syndrome. In an autopsied case of a 12 year old girl (McCune-Bruch, Sternberg-Joseph) basophilic hyperplasia with adenoma formation in the anterior pituitary and "mature" ovaries were observed, at 7 years of age one urine specimen had shown a high gonadotropin content and at 9½ years urinary estrogens had ranged from 48 to 288 IU (cf Table 1). (2) Achondroplastic dwarfism (Shelling). (3) Familial cretinism, girl 5 to 9 years old (Kendle). (4) Insulin injections in a nondiabetic girl aged 8½ years (Williams and Williams). (5) Presacral teratoma in a 9 month old boy (Rhoden). (6) Unverified tumor of the upper mediastinum, supposedly thymogenic, in a boy 11½ to 14½ years of age (1? Parkes-Weber). (7) Myxosarcoma of the prostate with metastases in a boy of 9 years (? Cowie).

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THE PHYSICIAN AND HIS OPPORTUNITIES FOR SERVICE TO THE UNDERPRIVILEGED AND HANDICAPPED CHILDREN IN HIS STATE

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LANDMARKS IN THE CARE OF CHILDREN

In the selection of my subject I had in mind a full appreciation of the services rendered by American medicine, in services to our armed forces and the public at large, during the recent eventful war years.

In the last years of the nineteenth century and the early years of this century great progress was made in the reduction of both infant and child morbidity and mortality.

A brief review of a few of the landmarks in our progress is necessary to bring to us a full realization of the profound advances made, by introduction of many life-saving measures, in the care of children during that period.

One epoch making example was the introduction of the use of antitoxin in the treatment of diphtheria in Von Bergman's Clinic in 1891. It was not until 1896, however, that the first publication of definite beneficial results was made. In 1896 deaths from diphtheria averaged from 50 to 145 per 100,000 population, and many physicians still decried the use of antitoxin as late as 1902.

In the year 1895 Roentgen introduced the use of the x-ray as a diagnostic measure; its therapeutic application came later. Dysentery and tuberculosis were the outstanding scourges of the infant world. Pasteurization came much later. The first Milk Commission in Chicago was established in 1903.

Dr. Isaac A. Abt, in his recently published autobiography, "Baby Doctor, Fifty Years of Child Care," tells the story as only he could, of the opposition met by our Chicago Milk Commission in our efforts to overcome the short-sighted policies of Chicago milk dealers who attempted to prevent the passage of an ordinance for compulsive pasteurization of milk.

Neither the public in general nor the mayor showed any great enthusiasm for our project. Attempts at legislative regulation failed repeatedly because of the pressure of the small milk dealers, who felt that they could not pay the price of cleanliness.

My speech evoked catcalls and a display of fists and Alderman Hay who led the opposition, retorted by denouncing all reformers, and in particular a man named Abt, and tried to engage me in debate.

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"I don't care to enter into any personal discussion with you," I replied, "I came to this meeting to represent the people and protect the lives of their babies."

The response to that statement was another demonstration by the milk dealers, and shouts of "Put him out! Put him out!"

Altogether it was a lively session, but I always enjoyed a good fight for a good cause, and this time I had the satisfaction of being on the winning side. It was not long before we got a new ordinance.

With the gradual improvement of the milk supply we saw a marked reduction in the incidence of tuberculosis, septic sore throat, and typhoid fever. Then, in 1911, the name Milk Commission, which was no longer completely descriptive of the aims of the organization, was changed, and it was decided to include in our program prenatal care, medical examination of babies, and advice about breast feeding and the preparation of milk formulas in the home. Thus began the Infant Welfare Society of Chicago.

These quotations from Abt tell the story of some of the early efforts of a profession to engage in *broad health promoting activities* in a metropolitan city.

I think we can agree that an equally broad program was that of immunization, first against smallpox, next diphtheria, later to include pertussis, tetanus, typhoid fever and the dysenteries. It will be difficult for the younger generation to realize the opposition we had to overcome when in 1917 the Board of Health of Chicago first proposed universal early immunization against diphtheria. Unfortunately, many doctors as well as the public were represented in much of the opposition to the many problems which confronted the forward looking medical pioneers of only fifty or fewer years ago. I need not go further into the vast field of preventive and curative medicine of the past half century which is well known to all of us.

Although World War II has come to an end, this does not imply that there will be peace on earth for the great multitude of our own citizens, and to a much larger extent for the masses of many other countries. I will not attempt to deal with the latter group, their salvation lies in the hands of their own governments with possibly such help as we of the United States can spare for them. They are the millions of children of other nations who have suffered from hunger and disease. They represent the displaced children, those orphaned and homeless who have further suffered severe emotional shocks. They should have our deepest sympathy.

RECENT PROGRESS

Having thus far spoken largely of past accomplishments I now emphasize the fields for assistance to children which lie before us and which should intrigue both our imagination and our activities. My special thought is for our children of today and tomorrow. In the selection of this field for thought I have had in mind the time and effort which the members of our profession are giving to promote the welfare of the

coming generation of adults, the boys and girls of today, so that it need not be stated that well over 25 per cent of the young males and females of our nation have physical or mental handicaps which make them ineligible for services in the Armed Forces of our country.

On whom did the odium for such a state of affairs fall? Certainly by far the greater number are the result of heredity or family neglect, however, our own medical records were none too satisfactory. I am not referring to those children whom we see in our private consultation rooms but more generally of those families able to provide medical care but who do not have the intuition to foresee the results of neglect of their own children and more especially of the underprivileged and handicapped children to whom the means of the best medical attention, care and schooling have not been made available.

Clinical experience leaves no doubt but that *the young infant* of today is being given a good chance, not alone for survival but also for good physical and mental development.

Due to the more recent impetus given to programs instituted for the care of *the premature infant*, the most dependent group of infants, the progress made in meeting their requirements represents another advance. A few facts will illustrate the thought that has been given to them so that they may have better opportunities for physical and mental growth.

According to reports received by the Children's Bureau, twenty-one states, Hawaii and Alaska, have already made or have submitted plans for the care of premature infants as part of their maternal and child health programs under the Social Security Act. In general, the programs developed by the states to deal with the problem contain three main divisions, an educational program, the provision of field nursing services and the provision of equipment in the form of incubators.

In addition to these educational efforts which are basic, some health departments have provided the services of public health nurses to assist practicing physicians to care for these infants in their homes when necessary and more especially to teach members of the family the special methods necessary for their protection. A few states have made provision for pediatric consultant services for rural districts.

In many cities throughout the United States there have been developed city-wide plans for the care of premature infants. In some cities there is provided a twenty-four hour ambulance service for the conveyance of infants to hospital stations when that is considered necessary. Special stations for their care have been established and oxygen and other types of emergency therapy are available. Nursing service in the field and in the hospital are rendered by personnel with special training. This is essential to any successful program.

Mother's milk stations, from which breast milk is supplied, have been established in a number of cities. Visiting nurse service can be

of inestimable value in encouraging the mother to keep up her breast milk in the home so that the infant may be returned to its home at the earliest possible date. Further instruction of the mother through early visits after the infant is brought to the station is also given and a visit preceding its return to the home. These are not alone valuable to the mother but mean security for the infant when it is returned to the family.

In large cities, outpatient clinics are maintained for instruction of the mothers and the care and supervision of graduates from the station who do not have private physicians. Many states and cities also provide a simple type of heated bed that can be loaned to the family.

There is still a great field open for the providing of further facilities.

The *school age child* had benefited by school health examinations, but the *preschool child*, on the whole, represents a much neglected group, both as to nutrition and physical development. It is to this large group of runabouts that we as physicians must give our serious attention.

CHILD HEALTH IN THE POSTWAR PERIOD

More recently a special committee for consideration of child health in the postwar period has been formed. The committee consists of three members of each of the following groups: The American Academy of Pediatrics, the American Pediatric Society, and the Medical Advisory Board of the Children's Bureau. They have outlined a course for procedure which is deserving of most serious consideration. From this report I am quoting:

A CONSIDERATION OF CHILD HEALTH IN THE POSTWAR PERIOD

It has been agreed that the Emergency Maternity and Infant Care Program shall end six months after the war.

OBJECTIVE

To make available to all mothers and children in the U.S.A. all essential preventive, diagnostic and curative medical services of high quality, which used in cooperation with the other services for children, will make this country an ideal place for children to grow into responsible citizens.

PROBLEMS

A large number of children do not receive preventive and curative care compatible with present day standards of good pediatric care because:

- I The services are not available where they reside,
 - II The parents are unable to pay for the services,
 - III There is an unwillingness to use, or lack of knowledge of available facilities.
- I The services are not generally available where they reside because of lack of:

PERSONNEL

Physicians

As private practitioners among children in the United States 2536 pediatricians are taking care of from 10 to 20 per cent of the child population in their communities, 96.4 per cent of these pediatricians are practicing in communities of over 10,000 population. The remaining 80 to

- 90 per cent receive preventive and curative care of varying quality from general practitioners and public health agencies.
- The need of increased facilities for better training in pediatrics in medical schools and hospitals, particularly in the post war period
- The need of more adequate training of pediatricians in the field of mental health
- The need to educate the general practitioner to give better pediatric care
- The need to increase the number of men entering the specialty of pediatrics

Nurses

Public Health Nurses

- There is a need for the education and training of a greater number of public health nurses, especially those versed in the problems of child health
- For every 5000 inhabitants in a community there should be provided a public health nurse with an ideal ratio of one to every 2500 inhabitants
- The development of training centers for public health nurses especially is urgently needed for rural areas.

Pediatric Nurses

- There is need of nurses especially trained in the care of infants and children. Particularly to be emphasized is the care of the premature and the newly-born infants

FACILITIES

Hospitals There is a need of

- More beds for infants and children in general hospitals
- Better facilities for the care of premature and newly born infants
- The establishment of children's hospitals in association with general hospitals or medical school units is to be encouraged
- There is need of proper correlation of housing, education, recreation and nutrition with any program relating to child health

Education

- The present impasse in the jurisdiction of school health between Boards of Education and Departments of Health needs careful consideration by proper authorities at local, state and federal levels, in order to establish a working basis between these bodies for an adequate school preventive and curative health program. Attention needs to be given particularly to the improvement of school health services in rural communities, so many of which they are practically nonexistent.

Administration of details of Children's Health Services should be determined by physicians, agencies and the people at the local level as children's health care cannot be administered by remote control at the state or federal level.

The qualifications as to the admission to the Child Health Conferences should be determined at the local level.

THE ILLINOIS AND CHICAGO PROGRAMS

Having considered advances in child protection in the early years of this century, and some fields for future development, let us consider some of the fields requiring the wholehearted support of the medical profession and which all of us encounter in our daily practice.

Among the many three are of such importance that they call for the most serious thought and assistance of the medical profession in every state, county and city. These are (1) the underprivileged child (2) the handicapped child, and (3) the dependent and delinquent

children As concrete examples, I take the privilege of speaking of the cooperation on the part of the physicians of Illinois and Chicago in the enumerated fields In Illinois one-half of the total population of 8,200,000 reside in Cook County and within this county in the City of Chicago there reside an overwhelming majority of the county's population.

I Public Aid in Illinois to the Underprivileged Child —In Illinois there are medical advisory committees representing the state, counties and cities, serving with the respective Boards for Public Welfare In Cook County and Chicago the same committee of six have served for twelve years For the state three members of our Chicago committee have served with three downstate members over the same period of time All appointments are made by the state, the county and the local medical societies

Through the interlocking of these committees the activities in the individual counties and towns, and the state as a whole, have developed a fairly uniform understanding of the medical needs of our indigent population Through the willingness of the medical profession to be of assistance in handling the many difficult situations that have arisen in caring for the needs of so large a group of dependents, there has developed a fine feeling of mutual confidence between the officials responsible for public welfare and the medical profession

Our state and local medical society committees have assumed the responsibility of disciplining their own members, when complaints are brought to them by the officials responsible for the program or by the recipients of assistance

In 1939, during the period of greatest distress, under the Chicago Welfare Administration 253,510 were receiving relief, of which 108,249 were children under the age of 18 years In the month of April 1945 these figures had dropped to a total of 28,364, of which 13,558 were children

In October 1941 the program for the Aid to Dependent Children was initiated and in the month of April 1945, 20,070 children were enrolled in Chicago for payment either through Aid to Dependent Children or Mother's Pension grants It is expected that this enrollment will in the future show a decided increase

The principle of free choice of physicians, and so far as possible the selection of the hospital, is followed by the Chicago Welfare Administration and the Illinois Public Aid Commission

The physician in every community should feel a responsibility for the proper function of such programs and take an active interest through his County Medical Society in which largely rests the responsibility for the functioning of these programs In Chicago more than 2500 doctors have volunteered for this assistance on a decreased fee basis

2 **Services to Handicapped Children**—For eight years as a member of the Medical Advisory Board to the Division of Services for Crippled Children, which in the past two years has been transferred from the Department of Public Welfare to the University of Illinois, I have seen it broadened in its field of endeavor to include paralysis from cerebral and spinal causes, rheumatic fever with arthritis and cardiac complications, speech defects, and the mentally handicapped.

The Division is prepared to render all necessary services where the child's family is unable to provide them through its own resources, and granted the child is suffering a condition which lends itself to treatment. A criterion of eligibility is that the child must be educable. These services reach into every county and community in the state.

The services of the Crippled Children's Division are complete. In short, every medical and related specialty necessary to the complete care and rehabilitation of the patient is employed.

Special attention is now being given to the development of educational programs for cerebral palsied or spastic children. I feel that they present the most heart-appealing group of all children. On June 18, 1945, the State Senate in Illinois appropriated 420,000 dollars for the care and education of spastic crippled children. Why we have been so long in appreciating the needs and furnishing the necessary schooling and medical attention is difficult to answer.

Recently I spent a part of two days with Dr. Earl Carlson at Pompano, Florida, where his winter school for spastics is located, his summer school is at East Hampden, New York. He himself is a severe spastic who through his own perseverance, notwithstanding his handicaps graduated from Yale University School of Medicine. He has established schools complete in all details for individualizing the needs of these children so that they may become self-supporting and useful citizens.

The handicapped, like other persons, have a right to an academic and cultural education, and not merely to one that is vocational in nature, though the latter should also be provided.

3 **The Dependant and Delinquent Child**—It is the responsibility and function of the Illinois Board of Public Welfare Commissioners to inquire into the equipment and management and policies of all institutions and organizations coming under the supervision and inspection of the Department of Public Welfare and the Department of Public Safety.

As a member of the Illinois Board of Public Welfare Commissioners through twelve years under different administrations we have witnessed great progress in the care of the average population, some 45,000 cared for in our state institutions. Let it be said that there is still room for much improvement, we are still far from the standards to be hoped for.

Among our state schools there are eight which are classified as children's institutions—two care for the mentally ill and epileptic children, three house the delinquents committed by our juvenile court, one each for the deaf and blind, and the Soldiers and Sailors Children's School for the care and education of veterans' children. The latter school, which has had an average enrollment of from 600 to 800, is of great interest to the members of the American Legion and the Veterans of Foreign Wars. It is expected that this enrollment will increase as it is largely dependent upon war casualties.

In Illinois our Governor appoints an *Advisory Board on Delinquency Prevention*. The membership consists largely of county judges, state officials, interested lay citizens, and members of the professions. My interest in this board has been stimulated by my contacts with Judge Frank H. Bicek of the Juvenile Court of Cook County, a branch of the Circuit Court through which our delinquent boys and girls are committed. In Chicago this court daily passes on an average of 120 cases but not all are cases of juvenile delinquency, in fact, a large percentage are dependents. However, in 1944, 2052 new petitions were filed in delinquency cases. Of these, 1617 affected boys and 435 girls. Fortunately, through the organized efforts of the Court and the Social Services, both professional and lay, less than 1 per cent were held to the grand jury, the others remaining under observation or placement under the jurisdiction of the court.

When the judge decides that the best interests of the child and the community will be served they are sent to the Juvenile Detention Home where they are given a complete physical examination and, when indicated, a psychiatric study is made. Unfortunately, in the past many dependent children were committed to state institutions, more especially from small downstate counties, because in the absence of proper housing facilities county judges had no alternative. *Today, foster homes* offer a most desirable solution for dependent children and those guilty of minor offenses whose homes are unsuitable for their protection.

Today every county in Illinois is organized in an effort to prevent juvenile delinquency. The urgency for such organization is only too evident in these days of broken homes and changes in the family life brought about, in part at least, by the conditions related to war.

OUR DEBT TO SOCIETY

I have sketched some of the many civic activities having to do with the general welfare of the community which are open to the thoughtful physician. Only too often do we fail to note the requirements of the child in its everyday life and allow ourselves to be more attracted by the more visionary problems.

It must be recognized that if the members of the medical profession in practice do not influence the line of thought in our com-

munities, both state and local government will do it for us and federalization of practice will remove the strong incentives in our lives which made possible the great contributions to medicine by the members of our profession which have preceded our time

It must be left to the individual physician to find the outlets for service most suitable to his talents and skills. The fulfillment of the needs of his less fortunate neighbors will mark him as an outstanding member of his profession. The counterpart of the services for children in Illinois are to be found in every state, county and city in the United States

THE FUTURE

There is still great progress to be made. Through all changes in practice which may come we must *retain* our ideals for freedom of thought and action. We cannot afford to lose sight of the fact that the individual is the cornerstone of the nation. We must not forget that patients are human beings and that the third generation of the great are often those who seek alms tomorrow, that in reading of the great feats and sacrifices of our armies those names among our heroes are of every nationality and every stratum of society—quality is what counts in the final analysis.

Never as before our colleagues are being acclaimed as great humanitarians.

"All Americans want this country to be a place where children can live in safety and grow in understanding of the part they are to play in the future of our American Nation "

CLINICS ON OTHER SUBJECTS

A NEW METHOD OF TREATMENT OF DUPUYTREN'S CONTRACTURE, A FORM OF FIBROSITIS

CHARLES LEROY STEINBERG, M D, F.A.C.P.*

BARON M Dupuytren,^{1 2} in 1831 described his careful dissection of the palmar fascia in an autopsied case of the disease which bears his name. He recognized that the flexor tendons and their sheaths were unharmed but that the flexion contracture was caused by the fibrosis of four fibrous slips originating from the inferior margin of the palmar fascia. These slips bifurcate at the distal ends of the four lateral metacarpal bones and each branch of the bifurcated slip passes on to be attached to the side and not to the front of the phalanx. The flexor tendons pass through the hiatus of the bifurcated slips. The wrinkled state of the skin resulted from various fibrous filaments passing from the fascia into the integument. Dupuytren described the successful treatment of this condition by the transverse section of these slips and of the fascia which furnish them. He recognized trauma as the etiologic agent.

He described the four larger arches which enclose the flexor tendons of the lateral four fingers, but failed to identify the four smaller arches located opposite the interspaces. These smaller arches are known as the lumbrical canals and each encloses the vessels, nerves and a lumbricalis muscle. The palmar fascia and its septa undergo fibrous hypertrophy in Dupuytren's contracture.

Bunnell³ found that microscopic cross-section of the skin in Dupuytren's contracture showed great thickening of the cornified layer, thinning and flattening of the stratum mucosum and obliteration of the corium, which normally extends deep into the epidermis. This is the picture of scleroderma which is constantly present in the palm in these cases. Nothing but dense cicatricial tissue which has squeezed out all the fat and deeper structures of the skin is found deeper. Clumps of round cells are found scattered throughout the dense fibrous tissue. This tissue is more cellular and vascular in the early stages. Persistent flexion contracture causes secondary contracture of the skin, nerves and joint capsule.

The papers on the incidence of Dupuytren's contracture by Kanel,⁴ J. S. Davis,⁵ A. A. Davis⁶ and Meyerding⁷ suggest that Dupuy-

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tren's contracture occurs in 1 to 2 per cent of the population. The incidence increases in proportion to the age of the population. It is encountered more frequently in the rheumatic group of patients. It occurs frequently in the white collar workers as well as in heavy manual workers, and in those people suffering from coronary insufficiency.

Previous communications^{8, 9, 10, 11} have described the value of the tocopherols in the treatment of primary fibrositis. The group of known tocopherols (alpha, beta and gamma) occurs predominantly in plant materials. The best natural source is wheat germ oil. Varying amounts occur in other seed oils and rice germ oil. Lettuce and alfalfa contain

TABLE 1—VITAMIN E BLOOD LEVEL IN PRIMARY FIBROSITIS

Case	Vitamin E, Mg /100 Cc	Case	Vitamin E, Mg /100 Cc
1 E R	1 20	13 D S	0 95
2 M B	1 10	14 N H	1 41
3 S G	0 80	15 E I F	1 88
4 C S	0 93	16 G K.	1 11
5 C G	1 42	17 H T	1 65
6 R H	0 83	18 P R	1 22
7 J S	0 84	19 L B	1 16
8 A P	1 49	20 H C	1 20
9 M C	1 35	21 B H	0 75
10 G S	1 11	22 L C	1 30
11 C P	1 28	23 A W	1 40
12 A L	1 09	24 J R	1 56

considerable amounts, whereas fruits such as oranges and bananas contain small amounts. Animal fats including fish oils contain very little vitamin E. Somehow the animal uses up the vitamin E from plant life. It is known that animal life is unable to synthesize the vitamin even when the starting materials of the laboratory synthesis are fed to the animals.

The tocopherols are effective antioxidants. The vitamin E activity is in inverse proportion to their antioxidant power. Gamma tocopherol is the most powerful antioxidant but has the least vitamin E activity, beta tocopherol has the next antioxidant power, and alpha tocopherol has the least antioxidant power but the most vitamin E effectiveness.

Synthetic *d,l*-alpha tocopherol has the same biological efficacy as the naturally occurring tocopherol (2 to 3 mg correspond to one rat unit*). The beta and gamma isomers are only half as active as the alpha isomer (activity 5 mg). The acetate, propionate and butyrate esters are more active than the free vitamin. The phosphoric acid

* A rat unit is the smallest amount of vitamin E which when given orally daily to resorption sterile female rats for the entire period of gestation (twenty-one days) brings about in 50 per cent of the animals birth of at least one living young rat.

ester is more soluble and is therefore more active parenterally than the free vitamin.

Vitamin E can be accurately determined in the blood plasma by the method of Quaise and Harris¹² They found the blood plasma levels of tocopherols to be between 0.9 and 1.6 mg per 100 cc. with an average of 1.2 mg in a small series of healthy human individuals.

TABLE 2—VITAMIN E LEVEL IN SECONDARY FIBROSITIS

Case	Vitamin E, Mg/100 Cc.	Diagnosis
1 F V	1.27	Rheumatic Fever
2 B N	0.92	Rheumatoid Arthritis
3 E J G	1.16	Psychosomatic rheumatism
4 K. H.	0.87	Osteoarthritis
5 S K.	0.60	Rheumatoid arthritis (low income level)
6 A. D. N.	1.40	Rheumatoid arthritis
7 G K.	0.78	Chronic Gouty Arthritis
8. C. L. G	1.08	Rheumatoid Arthritis
9 M. G	1.19	Advanced osteoarthritis
10 A. U	0.99	Rheumatoid arthritis
11 P. L. a P	0.87	Rheumatoid arthritis
12. C. M	0.84	Gout
13 V H.	0.81	Advanced osteoarthritis
14 H R.	1.11	Rheumatoid arthritis
15 W F	1.41	Rheumatoid arthritis

The average plasma vitamin E level in twenty-four cases (Table 1) of primary fibrositis including six cases of Dupuytren's contracture was 1.21 mg per 100 cc. The lowest vitamin E level (Case B H) was in a case of Dupuytren's contracture complicated by early portal cirrhosis. The average plasma vitamin E level in fifteen cases of secondary fibrositis was 1.02 mg per 100 cc. (Table 2) One low value of 0.60 mg per 100 cc. was obtained in the case of S K. This was a

TABLE 3—VITAMIN E BLOOD LEVEL IN PORTAL CIRRHOSIS OF THE LIVER

Case	Vitamin E, Mg/100 Cc.	Vitamin A, Units/100 Cc.	Carotene, Micrograms/100 Cc
B H	0.75	53	29
G S	0.36	91	45

clinic patient whose diet was inadequate. Two patients suffering from portal cirrhosis (Table 3) had low vitamin E blood levels.

Not only is the blood vitamin E level low in portal cirrhosis but the absorption from the gastrointestinal tract is poor as shown by Figure 33. A dose of 1500 mg of natural mixed tocopherols containing 70 per cent of alpha tocopherol was given orally at 6 A.M. Blood levels were taken at 9 A.M., 11 A.M., 1 P.M., 3 P.M., 5 P.M. and the next

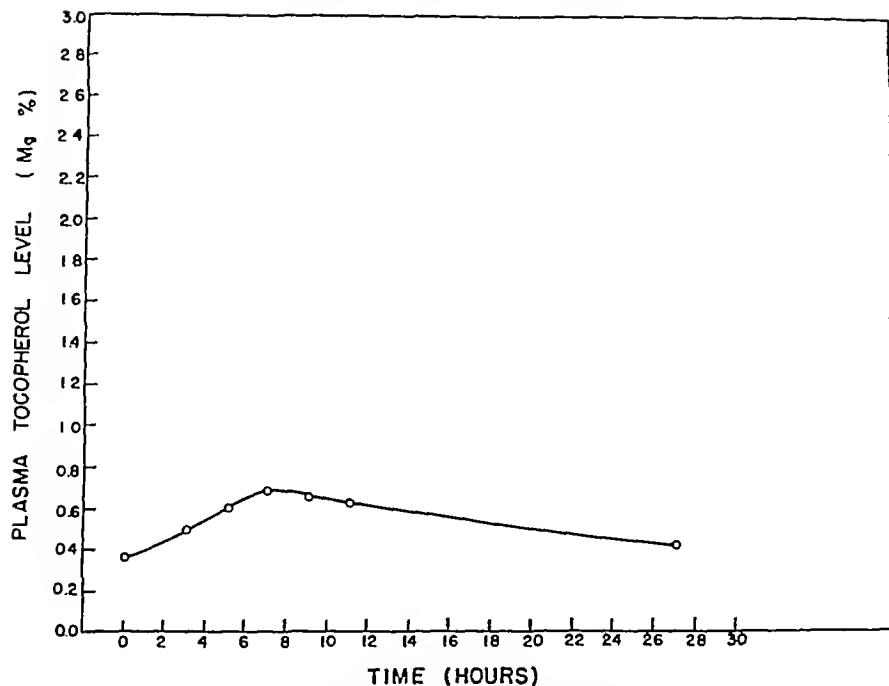


Fig 33 --Abnormal vitamin E absorption curve in a case of portal cirrhosis. The initial blood vitamin E level was very low, 0.36 mg per 100 cc of blood, and rose only to a height of 0.76 mg after the ingestion of 1500 mg of tocopherols

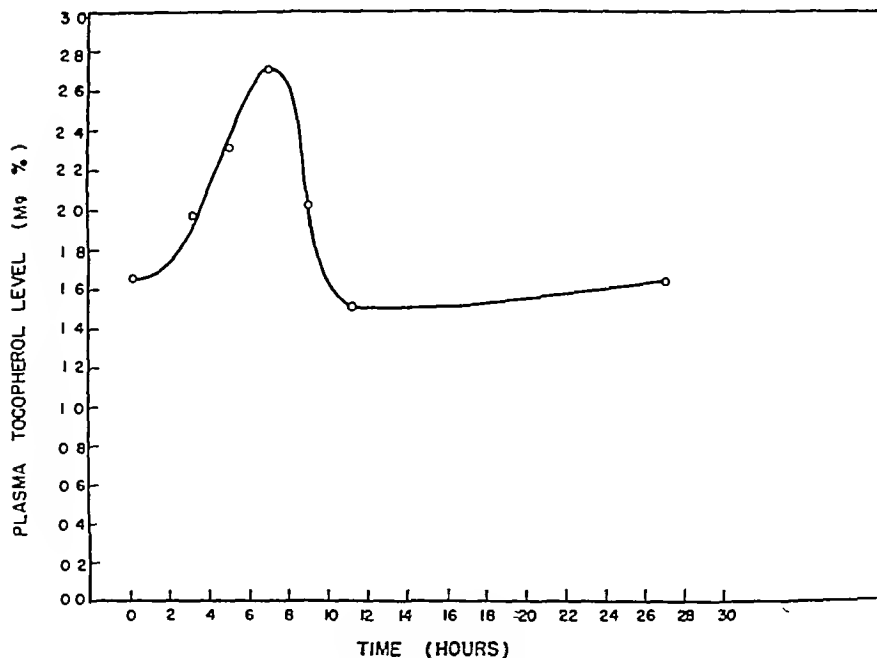


Fig 34 --A normal peak curve in the absorption of vitamin E

morning at 9 A.M. Figure 34 shows an absorption curve in a normal control and Figure 35 shows flat curves obtained in three cases of primary fibrositis. It may be concluded that the vitamin E blood level is normal and that the absorption of vitamin E is normal in primary fibrositis. There must be something abnormal in the tissue utilization. Similar conclusions regarding some states of vitamin deficiency have been reached by Spies and associates¹³ and by Govier¹⁴.

This abnormal tissue metabolism in primary fibrositis is indicated by creatinuria. Creatine studies were done on fifteen cases of primary fibrositis. The Folin microchemical method was employed. This method utilizes the principle that creatine on boiling with picric acid

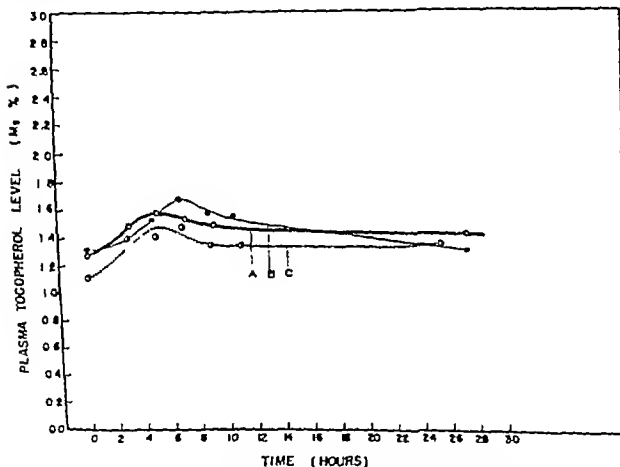


Fig 35—Flat vitamin E curves (A, B, C) in three cases of primary fibrositis.

is transformed into creatinine. By determining the content of creatinine before and after this transformation, it is possible to calculate the amount of creatine originally present in the urine. All patients were instructed to collect all the urine excreted from 8 A.M. one day until 8 A.M. the following day. The follow-up studies of the effect of tocopherol therapy were done in thirteen of these fifteen cases (Tables 4 and 5). It is of interest to note that the twenty-four hour urinary creatine excretion was increased in all cases before therapy was started. All these cases included patients having so-called "muscular rheumatism." The total amount of creatine in these cases varied from 264 to 918 mg. The creatine was increased above 300 mg. in twelve of these

cases Tocopherol therapy had a marked effect in reducing the urinary creatine excretion. In two instances the creatine excretion dropped

TABLE 4—THE EFFECT OF TOCOPHEROL THERAPY ON CREATINE METABOLISM IN PRIMARY FIBROSITIS (MARKED EFFECT)

Case	24 Hr Urinary Creatine before Therapy, Mg	Duration of Therapy	24 Hr Urinary Creatine after Therapy, Mg	Type of Treatment
1 E S	304	2 weeks	58	Oral
2 A A	495	1 week	110	200 mg alpha tocopherol I M every other day
3 P A	715	1 week	95	Oral
4 A P	728	1 week	876	Oral and 200 mg alpha tocopherol I M every 5 days
		2 weeks	822	
		3 weeks	800	
		5 weeks	640	
		6 weeks	588	
5 A DeV	690	2 weeks	140	Oral and 200 mg alpha tocopherol I M every 5 days
6 P T	706	5 days	418	Oral and 200 mg alpha tocopherol I M every 5 days
		2 weeks	594	
		3 weeks	462	
		4 weeks	453	
		5 weeks	460	
		7 weeks	196	
		11 weeks	90	
7 R B	378	1 week	255	200 mg alpha tocopherol I M every 5 days
		2 weeks	216	
8 A O	560	1 week	464	Oral only
9 A I	918	1 week	522	Oral and one dose 200 mg alpha tocopherol I M

TABLE 5—THE EFFECT OF TOCOPHEROL THERAPY ON CREATINE METABOLISM IN PRIMARY FIBROSITIS (MODERATE EFFECT)

Case	24 Hr Urinary Creatine before Therapy, Mg	Duration of Therapy	24 Hr Urinary Creatine after Therapy, Mg	Type of Treatment
1 C R	332	2 weeks	260	Oral
2 G S	306	12 days	240	Oral and 200 mg alpha tocopherol I M every 5 days
3 V McN	270	4 weeks	175	Oral
4 C B	264	2 weeks	185	Oral and 200 mg alpha tocopherol I M every week

from 715 to 95 mg and from 495 to 110 mg respectively after one week of tocopherol therapy, and in another instance the creatine ex-

cretion dropped from 706 to 196 mg after seven weeks' tocopherol therapy

TABLE 6—PRIMARY FIBROSITIS CASES WITH CREATINURIA (NO FOLLOW UP ON CREATINE EXCRETION)

Case	24 Hr Urinary Creatine Excretion Mg
1 M L	273
2 O McC	327

Most textbooks state that little or no creatine is to be found in the healthy male adult. The daily urinary creatine excretion varied from 86.4 to 140 mg daily in a control group of ten normal individuals (Table 7). Taylor and Chew¹⁵ found creatine in the urine of fifteen

TABLE 7—NORMAL CONTROLS

Case	24 Hr Urinary Creatine Excretion, Mg
1 C. R.	70 5 on one occasion 117 5 six weeks later
2 A W	103
3 S E.	97
4 L. M	140
5 M H	120
6 N W	117 5 on one occasion 97 2 two weeks later
7 A. B	136
8 A. H.	90
9 M W	86.4
10 M B	90

TABLE 8—CREATINE EXCRETION IN PROGRESSIVE MUSCULAR DYSTROPHY

Case	24 Hr Urinary Creatine before Therapy, Mg	Duration of Therapy	24 Hr Urinary Creatine after Therapy Mg	Type of Treatment
1 C S	504	1 week	309	Oral plus 200 mg. alpha tocopherol I. M every third day
2 C W	329	2 weeks None	302	

adult males in amounts varying between 0 and 196 mg per twenty-four hour period. Our method of creatine determination was also checked against a second group consisting of two cases of progressive muscular dystrophy in which the urinary creatine excretions were 504 and 329 mg respectively (Table 8).

Previous communications have described the effects of this therapy in fibrositis. One article¹¹ briefly reported the value of this therapy in Dupuytren's contracture. Seven more treated cases are reported herewith. One case, B. H., complicated by an alcoholic history and an early portal cirrhosis, was a failure (Fig 36). Advanced fibrositis was

limited to one flexor tendon. Typical scleroderma was present in the palm of both hands. The blood vitamin A was 53 units, the carotene

Fig 36



Fig 37A

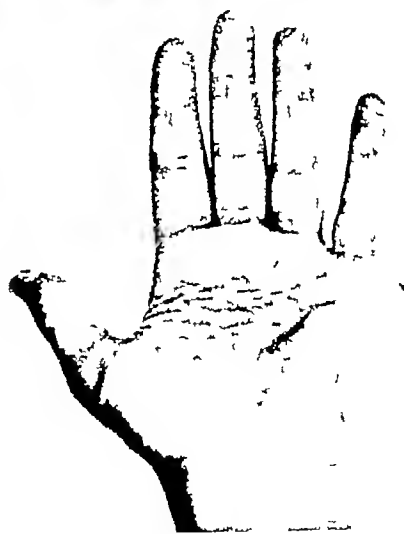


Fig 37B

Fig 36—(B H) Advanced Dupuytren's contracture with questionable calcification over fourth flexor tendon

Fig 37—(J R) Successful treatment of Dupuytren's contracture with vitamin E. A, Before treatment and B, after two weeks' treatment.

29 micrograms and the vitamin E 0.75 mg per 100 cc. The blood vitamin E rose to 0.87 mg per 100 cc and the carotene to 55 micrograms per 100 cc after forty-two days of therapy with 300 mg of vitamin E

daily. No clinical improvement occurred. The blood vitamin E was 0.97 mg per 100 cc. and the carotene 48 micrograms per 100 cc. after

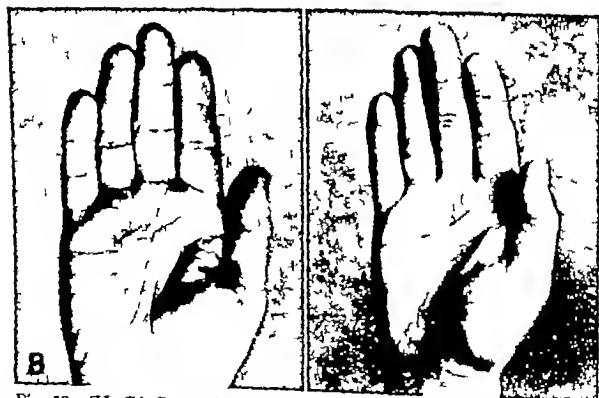
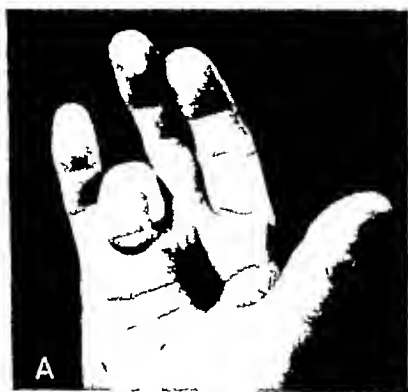


Fig 38—(H. C.) Successful treatment of Dupuytren's contracture with vitamin E after surgical failure. A, Before treatment, B, two weeks and C, four weeks after vitamin E treatment. Note disappearance of scleroderma in last two weeks of treatment.

fifty-five days of vitamin E therapy. The blood vitamin A had risen to 139 units per 100 cc. at this point. No clinical improvement occurred.

The six other cases of Dupuytren's contracture were cured with vitamin F therapy. In the cases of H. C. and J. R., 300 mg of vita-

min E were given daily by mouth Figure 37, A, shows the Dupuytren contracture in the former case before treatment and Figure 37, B, the results of two weeks' treatment, with complete cure In the case of H C, two weeks of treatment were required to alleviate the contracture and four weeks to cure the "scleroderma" Figure 38, A, illustrates the contracture in this case before treatment, B illustrates the case two weeks later and C shows disappearance of the wrinkled skin after four weeks' treatment The blood vitamin E levels before

TABLE 9 —VITAMIN E BLOOD PLASMA LEVEL IN DUPUYTREN'S CONTRACTURE

Case	Before Treatment	Duration of Treatment	After Treatment	Dose
1 L B	1 16	1 week 3 weeks 5 weeks	2 8 1 89 2 22	300 mg orally 300 mg orally 300 mg orally
2 H C	1 20	No estimation, while under first 4 weeks' treatment After 2 weeks' maintenance	1 32	50 mg daily
3 B H	0 75	42 days 55 days	0 87 0 97	300 mg orally daily 300 mg orally daily
4 E F	1 83	No follow up estimation		300 mg orally daily
5 J R	1 56	No follow up estimation		300 mg orally daily

and during treatment are shown in Table 9 Cases C P, E I F, B H and J B were similarly treated and cured Case B H passed his Army physical examination and has been in the service eighteen months

SUMMARY AND CONCLUSIONS

1 Vitamin E is of value in the treatment of early and moderately advanced Dupuytren's contracture No surgery is required in these cases Surgery is indicated in prolonged cases in which the contracture has caused permanent changes This is particularly true if calcification has occurred Vitamin E should be used in conjunction with surgery in such cases

2 The optimum dosage is 300 mg of vitamin E daily given in divided doses of 100 mg three times daily until maximum improvement occurs and then a maintenance dose of 1 mg per kilogram of body weight

3 The blood plasma vitamin E level is normal in primary fibrosis The plateau curve obtained in vitamin E absorption experiments and the creatinuria indicate abnormal tissue utilization of the vitamin

4 Extensive liver disease such as is found in portal cirrhosis affects both the absorption and storage of vitamin E Vitamin E, being a fat-soluble vitamin, behaves similarly to vitamin A

5 An inadequate diet may account for a low vitamin E level

6 No untoward effects have been obtained from oral vitamin E given over a period of three to four years in a maintenance dose of 1 mg per kilo

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SOME UNFORTUNATE PUBLIC HEALTH ASPECTS OF GONORRHEA CONTROL

P S PELOUZE, MD *

THERE IS in the country what is somewhat expansively called a "Campaign for the Control of Gonorrhea" which certainly is not controlling and, down where the patient and the doctor meet—or should—it is not really much of a campaign—in most of our communities, large or small. It lacks in initiative, enthusiasm and the will to do a good job. It stumbles, fumbles and lets a lot of easily overcome conditions cause it to hold up its hands and say, "What's the use?" As a real program for the protection of the public health it is as full of needless holes as a coal sieve is full of useful ones. And, saddest of all, it is assuming for us a veritable superepidemic where now only an epidemic exists.

Late in 1943 I wrote an article that appeared in the March, 1944 issue of Venereal Disease Information entitled "Gonorrhea The Epidemic We Face" It created quite a lot of adverse criticism both in and out of the Armed Services. There had at the time of writing the article been no rise in the number of infections in the Armed Services. In fact, they were boasting of the lowest rates in their histories, and justly so. In January, 1944 there occurred rather a sharp rise in rates and, sad to say, they are still rising.

It required no great foresight to see what was bound to occur. The country had been rather well-strewn with symptomless gonococcus carriers of both sexes by our sulfathiazole fiasco. Symptomless men were transmitting gonococci, apparently attenuated, to women who developed no symptoms to suggest that infection had taken place. They, in turn, were passing gonococci to men who did have symptoms because the gonococci, through animal passage, had regained some of their former virulence. These individuals got sulfathiazole and at least 20 per cent of them became symptomless carriers and infected more individuals and so on and so on. It was all there for anyone to see who knew something about gonorrhea and the gonococcus and cared to look.

In the summer of 1944 the ratio of gonorrhea to *early syphilis* in the Army of Continental United States stood from six or seven of the former to one of the latter. It now (August 1, 1945) stands at ten to one and it is still rising. I know of states wherein Service reports of cases to the health departments run anywhere from ten to thirty cases of gonorrhea to one of *newly acquired syphilis*. There is an immense section of one state wherein, I am reliably informed, gonorrhea tops

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early syphilis by fifty to one I know of but one city-county health unit in the country where the reported rates of gonorrhea could match these proportions if the newly acquired syphilis were separated from all syphilis revealed

I have been repeatedly informed that the highest infection rate in whites of the military personnel occurs among the fliers, with the paratroopers coming a close second I also have it from responsible sources that within three weeks of the return of our soldiers from abroad their gonorrhea rates are three times as high as those of the fliers Unless we get very busy at finding and curing gonorrhea in our civil communities anyone safely can predict what is going to happen now that our boys are returning by the millions

General James McGee, former Surgeon General of the Army, said to me in February, 1942 that, "If the doctors in our civil communities would do a fraction of what the Army is doing to control gonorrhea we would have it licked" The General was correct except that he failed to say what fraction and, obviously, we picked one far too low to even start the licking The Services have done a phenomenal job, while we have courted that small fraction—or nothing They have reported to our health authorities the names or description, or both, of the women from whom their personnel acquired their infections In many places these women have been placed under treatment in such large percentages as to convince anyone of the enormous need for a far better type of epidemiology all along the line The secret to success lies in case-finding and cure but unless we of the profession take a more serious view of the matter and do, or allow others to do the contact-tracing, an enormous back-log of infection will always remain to keep the gonococcal pot boiling merrily for years to come

Numerous surveys have shown that, in different localities, anywhere from fifty to 100 per cent of the treated gonococcal infections are treated by practicing physicians Almost every state and local health department has tried to get them to report their cases Yet, I know of no state wherein the results have been of a cheering nature One only need look at the tabulations of reported cases of gonorrhea and syphilis appearing from time to time in Venereal Disease Information to see what it all amounts to In doing so he should remember that the syphilis columns include all types of syphilis, not just early cases

Since April 1, 1942 it has been my privilege to talk before most of the county medical societies in thirty states as well as Puerto Rico and the Virgin Islands I have visited almost countless clinics and laboratories and have talked to over 11,000 medical students in 51 medical schools Also, I have talked to approximately 9000 graduate nurses and investigators Unless he is decidedly stupid one who has had such an experience should have a pretty good idea of what is and is not going on So, if my remarks seem unduly critical, they cannot be called swivel-chair ideas They are neither exaggerated nor untruthful,

but the result of a rare opportunity of seeing how America handles this highly important problem—and it is not done very well

Considering that we now have the cure, it is obvious that the one great call is to find the hidden gonorrhea to treat. And if anyone thinks this cannot be done let him go to Memphis, Tennessee, where Dr Alonzo Brand is doing it. Not only is he doing it in the clinic group of patients but he has won 52 per cent of the physicians over to reporting and letting his staff do their contact tracing and refer the discovered cases to the physicians for treatment.

Let us imagine that all of the doctors in the country followed the example of Dr Brand's 52 per cent. Just what chance would there be of controlling gonorrhea? Certainly not very much under existing conditions. At least half of the quiescent infections in the female would be missed by our laboratories even if all the material for study were properly collected—which it most assuredly is not.

Every bacteriologist in the country knows that in the female cultures are from two to three times as reliable as smears and, yet, at least 95 per cent of our communities do not have the culture facilities available. So far as I know, and I think I would have heard of it if there were an exception, only one state in the Union, New Jersey, offers culture facilities to every physician in the state no matter where he may live. Started by Dr Daniel Bergsma and ably carried on by Dr Glenn S Usher and Mr Russell Stein, this program has met with the enthusiastic support of the medical profession. In a recent paper by Usher and Stein* it is of distinct interest in this regard to see the following

Culture positive—smear negative	48.5 per cent
Culture positive—smear positive	37.5
Culture negative—smear positive	14

In other words, just about half of the infections would have escaped detection if smears alone had been employed, as is done in all but a pathetically small number of laboratories. We demand of them the best of studies for every disease but gonorrhea and continue to let them give us the poorest for that. This often is made doubly poor by the personal equation of the microscopist and the large percentage of smears from the cervical canal that are too thick to be seen through. Added to this is a goodly percentage of vaginal and vulvar smears that are thrown aside as useless for study, as they should be.

There are around 3800 clinics in the country for the treatment of the venereal diseases and so far as syphilis is concerned, most of them are doing a case-finding and treatment job that is worthy of admiration. When it comes to gonorrhea, however, one can draw a definite line of demarcation between those in which cultures are employed and those in which they are not. In the latter scant attention is paid to this

disease The differences are so obvious as to almost scream for culture facilities in all of them if any progress is to be made in finding the vast horde of infected individuals now roaming at will to further spread the disease

It has been shown time after time that the most fertile source for finding gonorrhea is among patients being treated for syphilis and the reverse And, yet, hundreds of our clinics make no real effort to look for it, except in those few patients who complain of symptoms This, despite the fact that it is the consensus of those who have studied many of the promiscuous young girls accused of having infected our military personnel, that about 90 per cent of those infected have had no symptoms nor do they have any mucosal blemishes to suggest that gonococci are present

Most assuredly, the unwillingness or hesitancy of our laboratories to fill what is unquestionably their responsibility, is placing a wet blanket over the entire control program It discourages earnest workers in the field and kills initiative in those in high places

I have lately returned (July 25) from a tour of a number of states in an effort to get them to start a state-wide culture service Fortified with graphs and data on what Dr Brand is doing in Memphis and Dr Usher in New Jersey, I tried to do as good a job of salesmanship as I could During the trip I listened to more puerile alibies and it-can't-be-done-heres than ever should have been uttered upon such an important problem by so many otherwise intelligent men

I have returned after a lapse of one or more months to state laboratories and health departments where I had urged the need, only to find that nothing had been done about the matter or, at most, the bacteriologists were fiddling around covering ground experimentally that a little study of the literature would have shown how futile were the efforts And this in America where so many seemingly impossible things are done every day

Perhaps if they knew that thousands of earnest public health nurses and investigators view their laboratories as places where coins must be flipped to see whether they would send a positive or negative report and that they, largely, would give odds on a bet that it would be negative on the woman who has infected one or more men, it might stimulate their pride a little and bring action Heaven knows we need it Our profession might learn something of profit from the widespread conviction of these same nurses and investigators to the effect that, so far as any great interest in epidemiology is concerned, we are almost a total loss

If penicillin cured 100 per cent of the patients who get it would we reduce the incidence of gonococcal infections by that alone? As things are today, the vast majority of those who need it will never get it We can only do the job by enormously elevating our degree of
icion, looking for gonorrhea where it does not seem to be, insist-

ing that our laboratories give us their best instead of their worst and making full and intelligent use of the facility if or when we get it. We must develop the "from whom to whom" attitude, as Stokes says, and consider the patient before us as the least important part of the disease picture. We have him, but it is our duty to get under treatment the source of his infection as well as those to whom he may have transmitted his disease. In no other way can we avoid the tragic consequences of what, otherwise, lies ahead

Ample observation tells me that a change in attitude toward gonorrhea among many of those who are supposed to guide the destinies of a control program in their states is very much needed. Certainly here is a poor place for that defeatist frame of mind that was almost universal before we had the sulfonamide drugs. And, now that we have penicillin, it is even far less defensible. To sit idly by and say that this or that cannot be done when it is being successfully done elsewhere, is to blind one's self to his duty and his state's possibilities. These things can be done in every state, given the will to do, and they do not have to be done with a club. A little study of what is wrong and how others have overcome similar conditions will fit any venereal disease officer to do likewise. The more kindly it is done the more successful and lasting it will be. One does not sell ideas and keep them sold by methods that arouse sales-resistance at the start. A realization that we are dealing with kindly, gentle folks and not a lot of people determined to do the wrong things should help greatly all along the line. He who doubts this should make a trip to Memphis and New Jersey

because we lacked interest in the disease and the deep determination to do something real about the matter. Sporadic attacks here and there will not greatly change the picture. A concerted effort throughout the Nation which takes into consideration the great need for public enlightenment, an enlightenment which our profession is best fitted to give, will go far to vitalize the National program. Nowhere in such a program should we or our laboratories be found wanting. Let us not go into a long sleep as we did after World War I. Today we have the cure sans the therapeutic drudgery of the past with all of its disappointments and failures. Social taboos have just about disappeared and the field is open for an intelligent battle against this important communicable disease that has been so sadly neglected in the past.

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SYMPOSIUM ON PROBLEMS IN POSTWAR MEDICINE

FOREWORD

THE Medical Department of the Army, which celebrated its 170th anniversary in 1945, has ever been in the forefront in both preventive and curative medicine. Its work in the global war which has just been won has been outstanding. In no other war, and in no other army in this war, have there been more glorious medical achievements. In no previous war has the death rate from disease among troops been lower than the death rate due to injury. Moreover, in the war the deaths from battle wounds among men reaching hospitals have been reduced to a new low, approximately 3 per cent. These accomplishments must, of necessity, be shared with the general medical profession as there were only some 1000 medical officers in the Regular Army in 1940 whereas at the peak there were some 45,000 physicians in Army service.

There have been no widespread epidemics of disease in the Army in World War II except the high incidence of malaria in the South and Southwest Pacific areas during the earlier months of action in those theaters. But as a result of mosquito control, atabrine suppressive treatment and strict antimalaria discipline during the later years of the war the situation was well in hand. The advances in shock therapy and traumatic surgery have been phenomenal, the treatment of the venereal diseases has progressed to the degree that the number of days lost to duty because of these infections has decreased remarkably. The fatality rate from meningitis decreased almost to the vanishing point as a result of early recognition of the disease and prompt administration of appropriate therapy.

The necessities of war promoted the supply and widespread use of penicillin and DDT, and streptomycin was discovered by Dr. S. A. Waksman of Merck & Company. These drugs may well revolutionize both curative and preventive medicine. The evaluation of the sulfonamides has progressed with the result that a better understanding of

their shortcomings and fuller utilization of their effective range have been effected

Although the Second Service Command, consisting of the States of New York, New Jersey and Delaware, is far removed from the zones of conflict, the five large general hospitals, one convalescent hospital, two regional hospitals, and many station hospitals have provided an immense amount of clinical material on a small part of which the papers published herein are based. All of the topics discussed have application to the civilian practice of medicine. The authors have all worked under the direct supervision of the undersigned and great credit is due them for their willingness and ability to compile the several articles presented, especially in view of the fact that this was an additional extracurricular "job" accomplished in spite of current understaffing of the hospitals and the extra pressure put upon them to render medical care to thousands of sick and wounded soldiers returned from overseas theaters of operation.

C M WALSON,
Brigadier General, USA

TUBERCULOUS PLEURAL EFFUSION*

CAPTAIN DANIEL J. FELDMAN AND LT. COLONEL HOWARD P. LEWIS
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THE so-called "idiopathic" pleural effusion, when it occurs in the younger age groups, has long been considered to be largely tuberculous in origin. Pleural effusion is also recognized as an early sign of malignant invasion of the pleura, as a complication of pneumonia, rheumatic fever, renal disease, cardiac failure or inflammatory disease below the diaphragm. In these latter conditions the cause of the effusion is usually apparent, but it is in that group in which the effusion is the paramount disorder that tuberculosis is dominant. Often the significance of spontaneous pleural effusion is not given the serious consideration it deserves. Figures vary as to the percentage of pleural effusions that are tuberculous, but it is generally conceded that 80 per cent or more of them have this etiology. For this reason a pleural effusion cannot be dismissed lightly when the cause is not obvious, even though the effusion may be small and transient.

The frequent inability to isolate the tubercle bacillus from pleural fluid and the common failure to find visible foci of tuberculosis in the lungs by x-ray often lead the observer to believe that an effusion is not tuberculous or, if it is, that it holds minimal future significance for the patient. Numerous studies have demonstrated, however, that tubercle bacilli frequently are not recovered from the fluid of tuberculous effusions. For this reason a bacteriologically sterile fluid still carries the same import as one that is positive. Active caseous tuberculosis can exist in the lung and be directly responsible for the onset of effusion, and yet the fluid may remain sterile. These facts demonstrate the importance of following up these patients in the years after the occurrence of their initial effusion.

Tuberculous pleural effusion is generally thought to occur through a number of different mechanisms. Extrapulmonary lesions with direct invasion of the pleura, such as tuberculosis of the spine with abscess of the mediastinum, or caseous tuberculosis of mediastinal lymph nodes are not often responsible, but they should always be sought for. An effusion may be the result of pleural tuberculosis or active tuberculosis of the lung in the subpleural region. Direct invasion of the pleura from the lung can result from the liquefaction of an underlying tuberculous focus which either extends to and directly involves the pleura or ruptures through to the pleural space.

*From the Medical Service, Rhoads General Hospital, Utica, New York.

The antistreptolysin and cold agglutinin titers and the classification of the streptococci obtained from the throat cultures were performed by Dr. Colin MacLeod, Professor of Bacteriology, New York University College of Medicine.

Tubercle bacilli from an active focus in the outer portion of the lung may be carried to the pleura by the lymphatic flow, which in this region moves toward the pleura and the hilum. They may also be transported to the pleura by hematogenous dissemination from a pulmonary or extrapulmonary lesion. Hematogenous spread from a distant area usually results in bilateral pleural effusion, although unilateral effusions often occur by this route. The pleural exudate is the direct result of a tuberculosis of the pleura. For this reason tubercle bacilli may be recovered from such fluids more consistently than from the types which follow.

Tuberculous foci in the immediate subpleural area can provoke exudation by the phenomenon of "collateral edema" in the same manner that edema of subcutaneous tissue occurs over the region of a deep-seated infection. In this instance the pleura reacts with an inflammatory exudate which ordinarily is sterile to all bacteriological study, since no local tuberculosis of the pleura exists. Allergic sensitivity of the pleural membranes to the tuberculo-protein undoubtedly plays an important role in certain individuals who have become sensitized to it as a result of prior infection. How much this phenomenon contributes to the reaction observed in the various modes of infection is not entirely known, but there is little doubt of its influence and importance.

Most tuberculous effusions are thought to be associated with the post-primary stage of the disease and, therefore, are important warnings of the presence of active tuberculosis in the lungs or in the extrapulmonary tissues. The focus responsible for the pleural reaction may lie in the lung, in caseous mediastinal nodes or in regions remote from the thorax. Extrapulmonary sources of infection, from whence spread can be accomplished by hematogenous or lymphatic routes, must always be looked for when pulmonary disease is not obviously apparent. Lesions in the lung which provoke pleural effusion are usually exudative or caseous and are seldom productive. Consequently, the effusion has a grave significance as concerns the future prospect for active parenchymal disease.

We became interested in this subject when we observed the relatively high proportion of pleural effusions in troops who were returned to this country because of medical diseases of the chest. If these cases were all tuberculous, the incidence of pleural tuberculosis in relation to the total number of tuberculous patients was inordinately high. This finding caused us to wonder if some other cause might be responsible. The severe pleural thickening and fibrosis, as well as the chronic nature of many of these cases, seemed to contradict previous experience. Subsequent observation impressed us with the importance of this condition as a cause of prolonged disability and prompted us to investigate the cases that reached this hospital to determine whether they were tuberculous or whether other factors such as streptococcal disease, virus infections of the lungs or simple pneumonias might be

responsible. The study was encouraged and the protocol for the scheme of investigation was worked out by Col Hermann L. Blumgart, at that time the Consultant in Medicine for the Second Service Command

METHODS OF STUDY

In the investigation of these cases, the following selected procedures were carried out

- 1 Patients were given careful historical and physical appraisals with searching, continuous clinical observation
- 2 The sputum was examined for tubercle bacilli by smears, cultures and guinea pig inoculations
- 3 The fasting gastric content was examined for tubercle bacilli
- 4 A thorough examination of all obtainable pleural fluid was made by the usual methods, including culture and guinea pig inoculation
- 5 Serial x-ray examinations of the chest were given during the period of observation.
- 6 There were weekly estimations of the sedimentation rate by the Wintrobe-Landsberg method. Normal values for males are 2 to 9 mm in one hour and for females, 2 to 20 mm. in one hour
- 7 Antistreptolysin titers were determined serially in a selected group
- 8 The cold agglutinin titer in the blood was determined in a selected number of cases
- 9 Throat cultures were taken to ascertain the possible correlation between the pathogens so obtained and the pleural pathology
- 10 Tuberculin tests were made on all patients

CLINICAL OBSERVATIONS

Fifty-nine patients with pleural effusion, admitted to this hospital between November 1943 and July 1945, were included in the group. The great majority of the patients had served in the European Theater, but cases were received from the Pacific and the continental United States. Many of the patients arrived in the resolving stage of the disease with only residual pleural exudate or pleural thickening of variable intensity. The results of pleural fluid studies, clinical findings and laboratory and x-ray examinations were available in the overseas records accompanying almost all the patients. A considerable number of acute cases in troops stationed nearby were also available for study. All the male patients were kept in one ward, whose personnel were specially trained in their duties. The clinical observation, all of which was carried out by the authors, was extremely minute and continuous.

Fifty-six of the patients were males and three were females. The ages varied from 20 to 47 years, but only five of the entire group were over 30 years of age. In thirty-nine patients the effusion was right-sided, in eighteen left-sided and in two bilateral. The presence

of fluid in the pleural space was ascertained by characteristic x-ray findings and thoracentesis in all patients. No fluid could be obtained from two patients because they were seen late in the course of the disease, but the x-ray and physical findings were so characteristic that they were included in the series. Twenty-one of the patients had pleural fluid present at the time of their hospitalization at Rhoads General Hospital.

Symptoms—The illness began in three rather characteristic ways. For thirty-four of the patients the onset was insidious, with mild prodromal complaints. For sixteen of the patients the onset was acute and followed a period of prodromal symptoms over various periods of time. Nine of the patients had acute fulminating onsets with no significant prodromal symptoms.

The first group exhibited a slow, progressive onset with general malaise, chronic cough, easy fatigability, the subjective sensation of fever and weight loss. After a period of time ranging from several weeks to months, dyspnea and pleuritic chest pain were generally noted, and eventually hospitalization resulted. In the second group, the onset of symptoms was similar to that described above but instead of a slow progression of complaints, a sudden increase in the severity of symptoms occurred accompanied by marked malaise, chilliness or chills, chest pain, cough, fever and considerable dyspnea. In the last group the onset was abrupt and severe with chills, high fever, marked malaise or prostration, cough and chest pain. Dyspnea usually ensued after several days of illness. The general appearance was that of a severe, acute, pulmonary infection.

Fever was noted in all cases. The height varied roughly with the severity, rising to as high as 105° F. in the more acute types. The febrile curve was irregular and variations of 3° to 4° within twenty-four hours were not uncommon. The high fevers would gradually drop over a period of seven to ten days in most instances, but a low-grade fever, particularly in the afternoon, would persist for weeks or months. After the temperature became normal, an afternoon rise was often observed if the patient became too active. In the patients whose onset was insidious, high fevers were not frequent, but a low-grade, irregular fever with a pronounced tendency toward afternoon elevation was observed.

The general appearance of the patients at the time of their admission to a hospital varied. Those in whom the onset was sudden and severe, were acutely ill. The clinical picture resembled an acute pneumonia, and an early diagnosis of atypical or lobar pneumonia was often made. Physical examination at that time frequently suggested consolidation in the involved side. The effusions were very often minimal at this time and x-ray studies did not clearly demonstrate their presence. Although in many instances it was recognized that pleural fluid probably existed, there was uncertainty as to whether or not an under-

lying consolidation was present as the primary cause of the illness. Penicillin and sulfonamide therapy was often instituted without benefit. Within a week of their admission most patients had developed a characteristic massive pleural effusion. Marked dyspnea was outstanding at this time. It was often necessary to remove fluid frequently in order to relieve respiratory embarrassment. During the period of high fever and acute illness the fluid tended to reaccumulate rapidly. In a few of the acute cases transient, mild splenomegaly was found during the active stage. One patient exhibited transient generalized lymphadenopathy as well.

In those patients whose onset was insidious, the clinical features were far less striking. The appearance was that of chronically ill patients. Unequivocal signs of pleural effusion were usually present at the time of admission. Dyspnea at rest and respiratory embarrassment were far less common than in the acute group, even when a large pleural effusion was present. This was undoubtedly due to the slow accumulation of the fluid which allowed adequate time for compensatory shifting of the mediastinum and emphysema of the unaffected lung tissue.

With prolonged bed rest and supportive therapy the acute symptoms disappeared and were replaced by complaints of easy fatigability, exertional dyspnea and failure to regain lost weight. These symptoms closely paralleled the period during which a low-grade fever was present, and were definitely increased with any activity. The last symptom to disappear was the easy fatigability, and this showed a great tendency to recur with any more than the mildest activity even months after the acute phase had ended. Chest pain on deep breathing, coughing or sudden movement persisted for excessively long periods of time.

In two cases with insidious onset, the patients developed fresh pleural effusions on the opposite side after the original ones had been absorbed. In both of these patients there was x ray evidence of hilar enlargement and suggestive parenchymal infiltration. In seven cases the effusion reappeared on the same side after clinical and x ray study had indicated complete absorption of the exudate and its replacement by thickened pleura. With these recurrences there was a resurgence of symptoms, and the entire picture as described above repeated itself. In one patient a massive ascites developed after a pleural effusion had disappeared leaving a thickened pleura of significant degree. The abdominal fluid revealed tubercle bacilli on culture. In another patient a subpectoral cold abscess appeared and pointed just to the right of the sternum after a left pleural effusion had been completely absorbed. Evidence by x ray of marked mediastinal widening appeared in this case as the effusion disappeared. Material aspirated from the abscess had the characteristics of tuberculous pus, but it was sterile to smear and culture. Early follow-ups have determined that at least two of the patients who were discharged from the service after prolonged hospitalization had recurrences of pleural effusion. In both instances a moderate amount of residual thickening of the pleura was present at the time of discharge but laboratory and clinical studies failed to reveal any signs of activity.

LABORATORY OBSERVATIONS

Blood counts on the patients studied at this hospital were within normal limits. Total and differential counts failed to reveal any constant variation, regardless of the phase of the illness. Occasionally a slight or moderate leukocytosis, with a normal differential count, was present very early in the disease, but this was transitory and not correlated with the clinical course. Serial blood counts during the convalescent phase of the illness were normal. No information of the activity of the disease was obtained by blood count studies.

The *sedimentation rate* was significantly elevated in fifty-five patients. In three the rate was normal upon arrival at this hospital, and no record of the test having been performed previously was available. Two patients had normal rates throughout. One of these two patients had a recurrence of the effusion on the opposite side, the other had tubercle bacilli in the gastric content and subsequently developed a parenchymal infiltrate. The most marked elevations in the sedimentation rate were seen early in the disease, and the rise tended to persist in varying degrees for long periods of time, closely paralleling the clinical course regardless of its severity. Frequently, abnormal sedimentation rates persisted after all symptoms had disappeared and the exudate had been completely absorbed. This was most marked in those patients who exhibited persistent pleural thickening. Upon resumption of mild activity, an elevation of the sedimentation rate often reappeared and warned of the recurrence of clinical symptoms. A rising rate seemed to indicate an exacerbation of the activity of the disease.

Skin tests with purified protein derivative (PPD) injected intracutaneously were performed in fifty-seven patients, fifty-six of whom showed positive reactions to either the 0.00002 mg or 0.005 mg dose. Two of the patients with positive reactions had negative reactions prior to the onset of their pleural effusion. No clinical correlation was noted between the degree of sensitivity to purified protein derivative and the severity of the disease.

Throat cultures were made in thirty-six cases to determine the possible relation between the organism so obtained and the primary disease. The organisms obtained varied considerably. A great majority were green-producing streptococci, and in some cases hemolytic streptococci were recovered. No significant correlation of these findings to the clinical condition was observed.

The *titer of cold agglutinins* was determined in twenty-three patients. Whenever possible blood specimens were obtained early in the onset of disease, and subsequent check examinations were made at intervals. No significant increase in titer was noted either at the onset or during the course of the illness in any patient. No important change in titer was seen in those cases in whom serial examinations were made.

Antistreptolysin titers of the blood were obtained in twenty-three

cases. Titers were determined in some of the pleural fluids and these were found to be essentially the same as those in the blood. Serial determinations were done in those cases seen at the onset, in those in whom severe exacerbations had occurred and in patients in a relatively stable phase of the disease. No persistent elevations of the anti-streptolysin titer were found. A few relatively high figures appeared in isolated specimens, but subsequent samples from the same patient showed normal levels after short intervals. Such incidental high values, therefore, were not considered significant.

Pleural fluid studies were performed in fifty-seven cases. The greater number of these fluids were originally studied overseas prior to the return of the patient to the United States. We examined the pleural fluid of twenty-one patients. In general the fluids were pale yellow to amber in color and were relatively clear or moderately hazy. No markedly cloudy, purulent or grossly bloody fluids were encountered. Specific gravities were all over 1.015. The protein levels varied between 3.5 and 6 mg per 100 cc. with albumin-globulin ratios similar to that in the blood. The fluid in a number of cases showed a marked tendency toward spontaneous coagulation in the test tube shortly after it had been withdrawn. This phenomenon generally appeared after the effusion had been present for several weeks or more, but in some instances it was observed within the first week. Large, stringy fibrin precipitates without complete coagulation were also seen usually presaging the complete coagulation of later samples. Because of this difficulty, samples of pleural fluid for cytological examination are now collected in a tube containing potassium oxalate.

Cell counts of the pleural fluid varied considerably, the total counts ranging from 100 to 2000-3000. Differential study showed a great preponderance of the lymphocyte series, 80 to 100 per cent of the cells falling in this group. In only six patients polymorphonuclear leukocytes made up 40 to 50 per cent or more of the total cell count in the pleural fluid initially, but later preponderant lymphocytosis appeared. No relationship between the total or differential cell counts and the presence of tubercle bacilli in the fluid was noted.

Cultures and smears of the fluid for pyogenic organisms were negative in all instances. Smears of the centrifuged sediment failed to reveal tubercle bacilli in all cases. Repeated culture of the centrifugate of large amounts of fluid on Petraghani's medium and inoculation of the same into several guinea pigs was done whenever possible. Where only a small amount of fluid could be obtained, the entire amount was cultured and injected into guinea pigs. Cultures were observed for eight weeks before they were considered negative. Guinea pigs were tuberculin tested prior to their use and were sacrificed after at least eight weeks. Such procedures were carried out repeatedly in the same patient when multiple aspirations were done. Not infrequently only one fluid specimen would be found positive by one of these methods.

out of several specimens from the same patient. Of the twenty-one cases so studied five, or 23 per cent, were positive for tubercle bacilli. In three patients the organism was isolated both by culture and in the guinea pig, in one by culture only and in another by guinea pig inoculation. A personal communication received from a military general laboratory in the European Theater of Operations, from an area where most of our patients had been evacuated, indicated that less than 25 per cent of the pleural fluids examined by guinea pig inoculation revealed the presence of tubercle bacilli.

Sputum examinations for tubercle bacilli were done on all of the patients. Earlier in the investigation these were twenty-four hour concentrates which were examined by direct smear. The results were so uniformly negative that a more intensive search was made in the cases studied later. In these the seventy-two hour pooled sputum was examined by smear, culture and guinea pig inoculation. One positive sputum was found in the entire group and this was positive by culture. Gastric secretion secured from fasting stomachs was collected for three days and studied similarly. Four patients were found to have tubercle bacilli in their gastric contents. In the positive cases the organisms were found either by culture or in the guinea pigs. In one of the four the smear was positive as well.

ROENTGENOLOGIC OBSERVATIONS

Chest roentgenograms of each patient were taken serially throughout the period of observation. Aside from the characteristic findings of pleural effusion, the changes preceding and following the acute phase were of the greatest interest. A notable thickening of the pleural membranes was observed in nearly all cases in which the fluid had not been evacuated and was allowed to absorb. When air had been introduced and the effusion was not subsequently removed, chronic localized areas of hydropneumothorax persisted, often for months. The initial pleural thickening, often as much as 4 cm in thickness, had an appearance similar to that of a fibrinous coagulum. Extraordinarily slow absorption of these plaques took place and it is of interest to note that in many of these patients the sedimentation rate remained elevated during most of the time required for their organization. Those patients whose fluid, when aspirated, developed a coagulum or a firm clot exhibited a high incidence of what was apparently a sudden and spontaneous clotting of the whole fluid mass in the pleural space. In several this solid mass extended from the topmost portion of the apex to the base and varied from 2 cm to as much as 4 cm in thickness. Organization and absorption of these coagulums was exceedingly slow and almost always resulted in a fibrothorax. In fifty-two of the cases studied there was x-ray evidence of pleural thickening to a significant degree. Complete, uncomplicated resolution occurred in only five of these patients during the period of our observation.



Fig 39 (Case 1) —Illustrates massive coagulation of pleural effusion. Three hundred cc. of fluid were secured after numerous thoracic punctures. The fluid removed coagulated spontaneously.



Fig 40 (Case 1) —Chronic pleural change still remaining three months later. Patient underwent acute febrile relapse one month prior. No fluid obtainable at this time.

The great majority of the films showed no evidence of parenchymal disease. Seven of the patients exhibited exudative parenchymal lesions by x-ray which varied in size from about 0.5 cm. to areas occupying about one-fifth of the involved lobe. They varied from small, flocculent, ill-defined shadows to dense-appearing, well-established parenchymal lesions. No relationship was noted between the lung containing the parenchymal lesion and the side on which the pleural effusion developed. In six of these cases the lesions were found in the upper third of the lung field, and in one the disease was basilar. In four cases the parenchymal infiltrate was present for some time before the de-

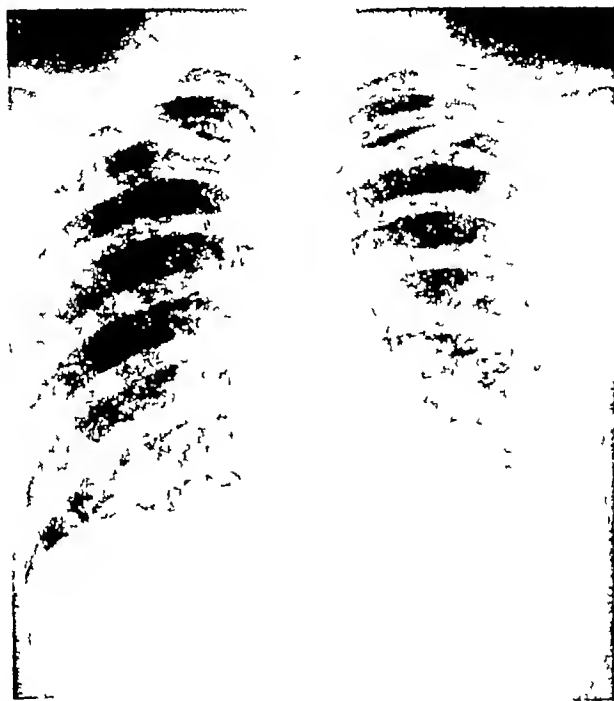


Fig. 41 (Case II) —Parenchymal infiltrate, left second and third interspaces anteriorly. First noted three and one-half months after onset of left pleural effusion. No clinical symptoms at this time.

velopment of the effusion. In one case it appeared during the existence of the effusion and in two was first noted after the effusion had been absorbed and the lung had been clear by x-ray for several months. Only two of the patients studied had discernible calcified areas. Tubercle bacilli were isolated in five of these patients from the sputum or gastric contents and in one from the pleural fluid.

The diagnosis of atypical pneumonia had been made in most of the patients in whom a significant parenchymal infiltration preceded the development of the effusion. In many others the hazy density at the base, combined with the mild atelectatic changes in the adjacent lung and the common hilar swelling on the affected side were thought to



Fig 42 (Case III) —Early left pleural effusion with associated infiltrates in upper and lower portions of left lung and accompanying left hilar enlargement. A diagnosis of atypical pneumonia was made at this time.



Fig 43 (Case III) —Three and one-half months later. The left pleural effusion has changed from left pleural effusion. No fluid obtainable. The left hilar enlargement has changed from left pleural effusion. No change in hilum and upper portion of left lung.

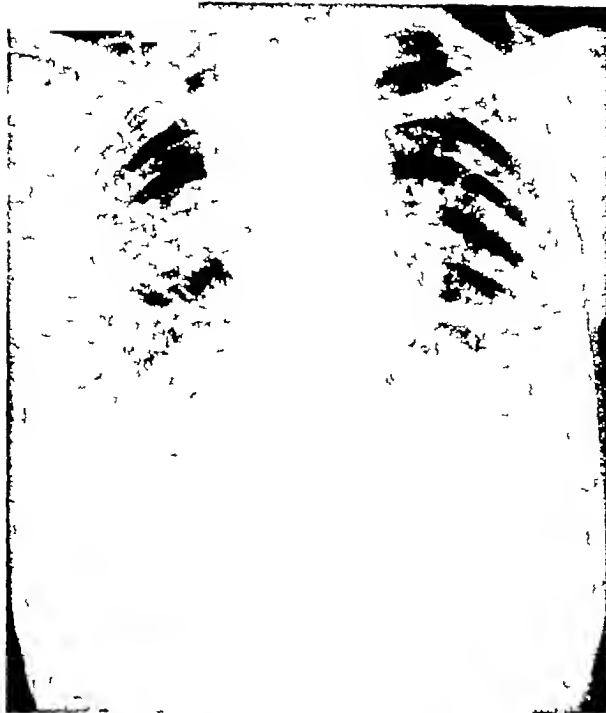


Fig 44 (Case III) —Relapse with high fever, hemoptysis and severe systemic manifestations fifteen days later. Note paramediastinal collection associated with a new right-sided effusion. Tubercle bacilli cultured from gastric secretion at this time. Pleural fluid sterile.



Fig 45 (Case III) —Residual changes, both lungs, one month later. Patient asymptomatic. Sedimentation rate high.

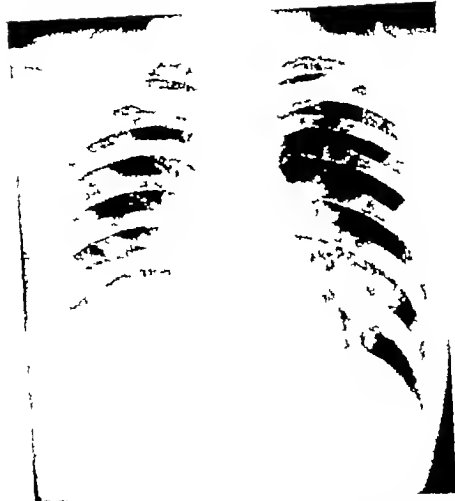


Fig 46 (Case IV) -Marked hilar swelling associated with pneumonitis, left lower chest and early pleural effusion, right. Admission diagnosis, atypical pneumonia



Fig 47 (Case IV) -One month later Right pleural effusion ill and febrile at this time. Tubercle bacilli recovered from sputum at this time.

be due to pneumonia. The subsequent effusion was often believed to be a postpneumonic exudate. In a number of patients the early clinical picture and roentgenologic findings were not incompatible with those seen in primary atypical pneumonia, and it is easy to understand why such a diagnosis would seem tenable.

Enlargement of the hilar lymph nodes was seen frequently. This enlargement was usually present in the early phases of the disease and was often transitory, persisting for a period of several weeks and then gradually disappearing. In a small number of cases the hilar enlarge-



Fig 48 (Case IV) —One month later. Residual changes of right pleural effusion. Small amount of pleural fluid obtainable. Gastric contents positive for tubercle bacilli by culture, and pleural fluid positive by guinea pig inoculation. Between figures 47 and 48, 2400 cc of fluid removed. Note persistence of lesions in left lung and hilum.

ment was marked and was accompanied by perihilar edema. The latter finding was much more persistent and was seen principally in those patients in whom parenchymal lesions were found by x-ray. In the films of those patients in whom parenchymal disease was noted prior to the development of fluid, the hilar component was striking and was greater on the side affected.

PLAN OF TREATMENT

The treatment of these cases was carried out according to the principles laid down by TB MED 71 of the Medical Department, United

States Army In the acute cases a sufficient amount of fluid was withdrawn (300 cc.) for diagnosis at necessary intervals The effusion was not otherwise disturbed unless pressure effects required withdrawal of some of the exudate The effusion was given the opportunity to absorb, but if after eight weeks it failed to exhibit any significant tendency to do so, it was then evacuated as completely as possible No air replacement was employed, but in a few instances a small amount of air was introduced in order to facilitate the study of the character of the underlying pulmonary tissue We have been impressed by the fact that, even with this relatively short delay in the evacuation of the fluid, in many instances chronic thickening of the pleural membranes or spontaneous coagulation of the whole exudate took place in that length of time.

COMMENT

The results of this study substantiate the opinion that pleural effusion which occurs in younger persons, in whom no other readily determinable cause for it exists, can be considered tuberculous until clear proof to the contrary is found While it is true that only a small part of our total patients were proved to have tuberculosis by recovery of the organism, nevertheless the marked similarity of all these cases has convinced us that all were tuberculous The prolonged and intimate observation which we were able to give each patient made it possible to eliminate many uncertainties in diagnosis.

Tuberculous pleural effusion is in every way as important a manifestation of active tuberculous disease as visible tuberculosis of the lungs or other organs. It carries with it the same implications as to future spread and disability as does active tuberculosis anywhere in the body Tuberculous pleural effusion demands the same care as active parenchymal disease, for active pulmonary tuberculosis may be the underlying cause of the effusion and may make its appearance at some future date after the effusion has resolved The incidence of frank pulmonary tuberculosis following pleural effusion is high, the figures of various authors ranging from 17 to 50 per cent The first five years, and particularly the first year, following the development of a pleural exudate are important in respect to the subsequent appearance of active tuberculosis.

The manner of onset of this disease can justifiably give rise to the belief that it is a condition resulting from pulmonary lesions other than tuberculosis The presence of an obvious inflammatory change in the lungs prior to the development of the effusion does not establish a nontuberculous etiology, as we have demonstrated In our patients the determination of the antistreptolysin and the cold agglutinin titers and the negative bacteriological studies for pyogenic organisms in the fluids would seem to eliminate to a large extent any cause other than tuberculosis. All our patients who exhibited a pulmonary infil-

trate, either prior to or coincident with the effusion, had considerable enlargement of the hilar lymph nodes. Hilar enlargement is not ordinarily a feature of the various specific and nonspecific types of pneumonitis, and this finding is a valuable one in suggesting a tuberculous etiology. The hilar enlargements seen in this region have not appeared to be malignant.

The sedimentation rate was valuable in determining the activity of the disease. It frequently suggested the presence of an active lesion in a patient who, by clinical appraisal, would be adjudged to have an inactive lesion. This has always been useful in judging the patient's response to physical activity. In a number of patients a rise in the sedimentation rate was the first warning of reactivation of the process. An increase in the sedimentation rate has been observed in patients who have been convalescent and completely free of symptoms for as long as two or three months.

Laboratory examination must be intensive and repeated if the maximum number of positive results are to be obtained. In our experience the examination of the three-day gastric specimens was the most satisfactory method for securing tubercle bacilli. Direct smear examination, culture on appropriate media and guinea pig inoculation should be performed on the pleural fluid, the pooled seventy-two hour sputum and the gastric secretions in all cases. Reliance on any one test has been shown to be unreliable.

The enormous thickening of the pleura seen in many of the patients has been unusual. The fibrin content of a number of the fluids has been high. Instances of spontaneous coagulation of the whole exudate with the formation of a solid, "jelled" mass extending from apex to base was most common when this phenomenon was observed. Numerous patients also developed thick coatings of what were interpreted to be fibrinous deposits on the pleural surfaces. These changes were by far most common in old cases in which the fluid was not evacuated. Fibrothorax with the subsequent development of diaphragmatic fixation and probable fibrosis of the underlying lung usually resulted. This group, as gauged by the sedimentation rate and the clinical response, exhibited an abnormally long period of activity of the disease.

There is a considerable difference of opinion as to the proper treatment of a tuberculous pleural effusion. There are those who advocate that only the fluid necessary for diagnosis be withdrawn and that the patient be permitted to absorb the remainder. Others believe that if absorption of the fluid does not occur within a reasonable time, all fluid should be evacuated in order to prevent severe fibrosis of the pleura and consequent injury to the underlying lung. Still another group holds the opinion that the fluid should be evacuated as soon as the acute febrile phase and the period of rapid reaccumulation has ended. According to this group the fluid should be completely withdrawn and replaced by an equal or nearly equal volume of air in

order to maintain a pneumothorax and to splint the mediastinum. Any reaccumulation of the fluid is removed.

It is clear that any patient with an underlying active pulmonary tuberculosis, whose effusion is allowed to resolve of its own accord, is exposed to the serious risk of adherence of the pleural surfaces, making the future employment of artificial pneumothorax impossible. This leaves available to the patient only the formidable procedures of thoracoplasty or extrapleural pneumolysis in case an advancing, uncontrollable parenchymal lesion appears. Failure to evacuate an effusion of any considerable size tends also to prolong inordinately the patient's convalescence.

It would seem advisable, in view of the foregoing, that after the febrile period has passed and reasonable stability in the effusion has occurred, which is ordinarily a period of two to three weeks, the fluid should be evacuated completely in successive stages if necessary, depending upon the size of the effusion. By this procedure the coagulation of large effusions can be prevented and the marked fibrinous deposits on the pleural surface can be avoided. Since the complete removal of fluid results in approximation of the pleural surfaces and thereby fosters their adherence, it would seem desirable that a pneumothorax of at least 200 to 300 cc be induced initially. Adequate x-ray observation of the underlying lung may then be made and, if necessary, collapse therapy may be continued. If proper aseptic technique is employed in all thoracic punctures, there is no reason to anticipate complication by secondary infection or undue changes from the introduction of air into the pleural space.

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ACUTE DISSEMINATED MILIARY TUBERCULOSIS

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ACUTE disseminated miliary tuberculosis may develop from the chronic forms of pulmonary or extrapulmonary tuberculosis, or it may erupt from some hidden and unsuspected tuberculous focus. In the former type the miliary spread may be a terminal event of chronic tuberculosis, in the latter type the symptoms arising from the disseminated miliary disease are the first indications of tuberculous infection. If there has been a recognized tuberculous lesion in the body, the development of the symptoms and signs of miliary spread do not offer too great a diagnostic problem, but when a healthy young adult presents the picture of an acute infectious process with nothing demonstrable to explain the cause of the illness, the true nature of the disease may be revealed only at the autopsy table. If the roentgenogram reveals miliary disease of the lungs the diagnosis is sure but when x-ray evidence is lacking the diagnosis can be arrived at only by a process of exclusion and even then doubt often exists as to the true nature of the morbid condition.

CASE REPORTS

The clinical histories of two patients are here reported who exhibited many of the signs and symptoms of typhoid fever, but who died of miliary tuberculosis as shown at autopsy. The roentgenograms of the lungs gave no inkling of miliary disease and confirmatory laboratory tests for typhoid fever or any other disease were lacking, which gave rise to much discussion as to the cause of the infectious process. A third case of the "typhoid type" of miliary tuberculosis is added for comparison in which the diagnosis was never in doubt because miliary disease was revealed by the roentgenograms of the lungs.

CASE I.—This 22 year old Negro soldier with thirteen months of service was admitted to the Station Hospital Camp Shanks, New York on March 5 1944. He had noted the first symptoms of illness about February 15 1944. At that time he contracted an upper respiratory infection and had noted some nonproductive cough for which he was treated at sick call. In addition he also complained of dizziness. He continued to feel poorly and applied for hospitalization on March 5. His temperature, on admission, was 102° F and physical examination at that time revealed no definite abnormality. The admission diagnosis was nasopharyngitis. The patient's previous history and family history were not remarkable and are irrelevant, apparently, to the present illness.

The patient continued to run a high fever and on March 9 sulfadiazine was started. At that time the patient had no evidence of pneumonia. His blood count on March 6 one day after admission, was as follows: 14.5 gm of hemoglobin,

From Halloran General Hospital Staten Island New York

5200 white blood cells of which 65 per cent were polymorphonuclears, 34 per cent lymphocytes and 1 per cent monocytes. The next blood count on March 11 showed 7600 white blood cells, with 68 per cent polymorphonuclears and 30 per cent lymphocytes. The hemoglobin at this time was 14.5 gm. On March 13 the patient's temperature was 104° F and he began to bleed from the nose. A nasal pack was introduced. On March 15 after three days of oozing from the nose, the blood count showed a marked anemia, namely 1,890,000 red blood cells with 6 gm of hemoglobin and a white count of 9600 with a normal differential. Sulfadiazine medication had been discontinued on March 13 as soon as the patient had begun to bleed. In addition to the epistaxis there were other evidences of a bleeding tendency. Petechiae were noted on the hard palate and several purpuric spots appeared over the right upper arm. The platelet counts, clotting and bleeding times, however, were normal. A smear of the blood showed changes in the red blood cells consistent with a rather acute anemia, to wit, basophilic stippling, hypochromia and poikilocytosis. Because of the pronounced fall in red blood cells and hemoglobin the patient was transfused on several occasions.

The patient's temperature during the last few days of his stay at Camp Shanks Station Hospital ranged between 102° and 104° F with remissions below 102° F. In addition to transfusions the patient received penicillin, 25,000 units intramuscularly every three hours for five days prior to his transfer to Halloran General Hospital. The chest x-rays revealed that the lung fields were clear but that there was a definite enlargement of the hilar nodes on both sides. On March 20 a palpable spleen was detected.

Upon admission to Halloran General Hospital the patient was acutely ill. His temperature was 103° F but he presented few physical signs. The findings on admission were as follows. The neck was slightly resistant but not definitely stiff. The eyeballs showed no abnormalities. The spleen was palpable about one to two fingerbreadths below the costal margin and seemed blunt and firm to the examining fingers. There were numerous expiratory squeaks and wheezes in both lungs. The blood count taken shortly after admission showed red blood cells 3,060,000 with 9.5 gm of hemoglobin, white blood count 5000 with 91 per cent polymorphonuclears, 7 per cent lymphocytes and 2 per cent promyelocytes. A careful study of the blood smear gave the impression of an acute infection of nonspecific type. The immaturity of the white blood cells was noted only in the form of promyelocytes, and no blast forms were seen. There were, however, moderate toxic changes in the polymorphonuclears. Because of the slight stiffness of the neck a spinal tap was performed and this yielded 10 cc of clear colorless fluid which was not under increased pressure. There were no cells in the spinal fluid and the Pandy test was negative. The total protein was 59.2 mg per 100 cc.

The patient's course in the hospital was characterized by a sustained fever ranging between 102° and 105° F with an occasional fall to 100° F. At no time was he cyanotic except at the termination of his illness. He had epistaxes at various intervals, but at no time was the blood loss from this source severe. The red blood count was maintained at a level of about 3,000,000 with 9 gm of hemoglobin and the white blood count did not vary materially from those records at the Camp Shanks Station Hospital. An x-ray of the chest at this hospital showed the enlarged hilar and mediastinal nodes (Fig. 49). Blood and urine cultures were negative. Stool examinations revealed occult blood on one occasion only. Cultures of the stools were negative for enteric pathogens. The Widal tests were negative.

After several days in the hospital the patient manifested hallucinations and delirium, and these increased up to the time of death. His fever remained high and the pulse rate averaged between 100 and 110 per minute. It was never dicrotic. On March 31 the patient's condition took a marked change for the worse.

He began to manifest generalized twitchings and spasmodic contractions of the muscles. He became totally disoriented and confused and lapsed into pulmonary edema. Emergency treatment of the pulmonary edema by means of venesection, application of tourniquets to the lower extremities, the administration of morphine and oxygen availed only to prolong the patient's life to the morning of April 1 at which time he died.

The medical officer in direct charge of the case listed the following diagnoses as the most probable: 1. Acute disseminated tuberculosis, although there were no tubercles in the lung fields and the eyegrounds showed no tubercles and the spinal fluid was normal. 2. Typhoid fever because of the sustained temperature, palpable spleen and confused mental state. No bacteriological or serological confirmation for this diagnosis was shown. 3. Aleukemic leukemia. This diagnosis could not be supported beyond the findings of enlarged hilar nodes.



Fig. 49 (Case I) —Showing enlarged hilar nodes.

and a palpable spleen and the hemorrhagic tendencies. 4. Acute Hodgkin's disease was considered but ruled out because of the lack of palpable superficial glands.

The postmortem examination showed miliary tuberculosis of lungs, liver and spleen and tuberculous adenitis of the deep cervical, mediastinal and abdominal lymph nodes. There was a cherry-sized nodule in the left lower lobe which was considered to be the pulmonary component of the primary complex. The pathologist believed this to be the origin of the disseminated lesions. Microscopic sections revealed central necrosis of the tubercles and acid fast bacilli were isolated from the tissues.

In summary, the patient presented the picture of a "typhoid state" — cachexia, delirium, muscular twitchings and tremors, epistaxis, high fever and palpable spleen, but not the classical slow pulse or leuko-

penia (although the white blood count ranged within normal limits of 5000 to 11,500) and none of the laboratory tests confirmed a diagnosis of typhoid fever

CASE II—This 28 year old, white staff sergeant with two years and ten months of service was admitted to Halloran General Hospital on January 12, 1945 as an evacuation patient from England. The soldier went on foreign service in July, 1942 and while overseas was ill on two occasions for short periods of time, once with a streptococcus sore throat and once with a urethral discharge which lasted but one day. In November, 1944 the patient became nervous and had crying spells and after hospitalization the diagnosis of psychoneurosis, anxiety state, was made and he was evacuated to the Zone of Interior on December 31, 1944. While on board the ship the patient refused to eat and after five or six days he developed chills and fever, running a daily temperature of 102° to 103° F., but he had no cough, diarrhea, abdominal pain or rash.

During the three weeks he was at Halloran General Hospital he ran a fever of 103° to 105° F with occasional dips below 101° F. No localizing physical signs could be found except that on occasions transient rales were heard at both bases. There were no abnormal neurological findings beyond a rather marked tremor of the muscles of the face and extremities. The spleen and liver were not palpable and the examinations of the fundi of the eyes were negative. The heart sounds were normal and no murmurs were heard. At no time were any petechiae, rose spots or other rashes noted. During the terminal days of his illness the patient had a slight icterus. He complained of abdominal distress and cramplike pains and occasional diarrhea. The abdomen was distended and tympanitic.

A composite report of the Widal tests ran as follows

	1 20	1 40	1 80	1 60	1 320	1 640	1 1280
E typhosa "O"	4+	3+	2+	±	—	—	—
E typhosa "H"	2+	2+	2+	2+	2+	+	+
Para A	—	—	2+	2+	2+	+	+
Para B	3+	2+	2+	±	—	—	—

Proteus OX19	} Negative in all dilutions
P. rularensis	
B. abortus	

Several blood cultures were negative as were the stool and urine cultures. There was a moderate secondary anemia. The white blood counts ran from a low of 3000 to a high of 10,000, the majority being around 5000. The differential showed a polymorphonuclear count of from 71 to 85 per cent, the rest of the cells being mostly lymphocytes. First and second strength PPD tuberculin tests were negative as was also the brucellergin skin test. The sedimentation rate was 38 mm. Several x-rays of the chest gave no definite indication of pulmonary involvement. The last portable x-ray taken on January 13 revealed very heavy truncal markings in the medial portions of both lower lobes (Fig. 50). While there was no positive evidence of consolidation in either lung field, there was a very questionable slight clouding of the medial portion of the right lower lobe. Lumbar puncture on two occasions showed normal spinal fluid. The eyegrounds were normal.

During the course of his hospital stay the patient received penicillin and sulfaiazine as well as plasma and transfusion of whole blood and parenteral glucose and amigen intravenously. The patient continued to have fever, delirium, marked generalized twitching of the muscles of the body and abdominal distention and toward the end he became comatose and died on February 3, 1945.

The autopsy revealed miliary tuberculosis of the lungs, spleen, peritoneum, liver, kidneys and adrenals. The tubercles were necrotic. *Mycobacterium tuberculosis* was recovered from the tissues. The mesenteric lymph nodes were enlarged and caseous. It was the pathologist's opinion that the dissemination of the tuberculosis came from these glands.

Summary—This patient exhibited all the classical signs and symptoms of typhoid fever with one or two exceptions. The pulse rate was high for typhoid fever. The blood counts averaged around 5000 and in one or two instances went as high as 10,000 although there was a low of 3000. The Widal tests were equivocal. Although the first dilutions showed an agglutination, at one time of 4+, as the disease



Fig. 50 (Case II)—Showing light clouding of lower right lung field

progressed the agglutinations did not become positive particularly in the higher dilution. Also no rose spots were found. The tuberculin tests in both first and second dilutions PPD were negative. The diagnosis of disseminated miliary tuberculosis was considered during the course of the illness as well as typhoid fever and brucellosis.

CASE III—This 23 year old white soldier was admitted to the Halloran General Hospital on July 12, 1944. He was too ill to give a clear history of his trouble and the history of his present illness and family history were secured from the record in his field medical jacket. His family history is revealing. His father died at the age of 38 of pulmonary tuberculosis. He was ill for one year of which time he was at home for eleven months and died November 15, 1940. The patient's mother is living and well and her x-rays have been reported negative. A sister aged 21 was found to have tuberculous lesions in April, 1944. Four

of the children of the family, two males and two females, are living and well. Their x-rays are reported as negative. The patient's paternal grandmother and two paternal aunts died of pulmonary tuberculosis. They had no contact with the patient beyond the age of 2.

In regard to the present illness the patient's field medical jacket states that he developed a headache associated with nausea and vomiting two days prior to admission to the overseas hospital which would indicate the onset of symptoms on June 5, 1944. There were no chills, fever, chest pains or abdominal complaints and no symptoms referable to any system. He was admitted to an aid station on June 7, 1944 with a temperature of 101° F., headache, nausea and vomiting. The diagnosis was undetermined. Further questioning of the patient at that time revealed that he had no recent weight loss. He had had no cough or hemoptysis, but his appetite had been poor. His fever remained high. A

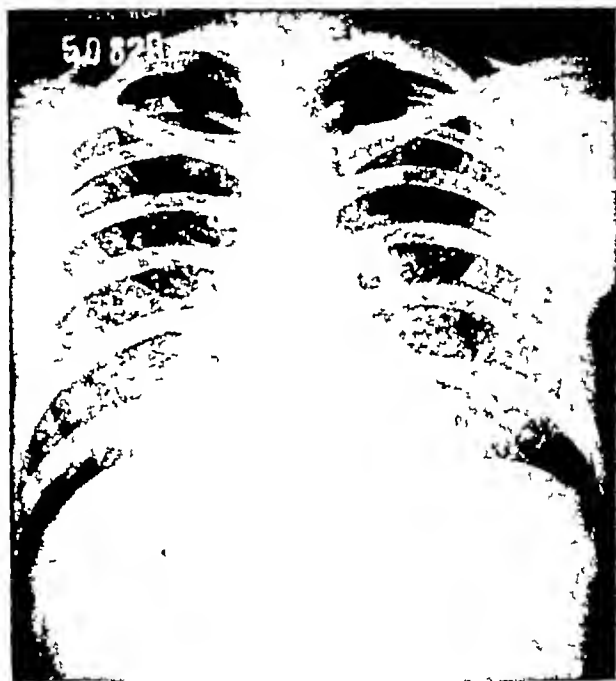


Fig. 51 (Case III) —Showing miliary disease of both lungs

heterophile antibody test was reported negative. Blood cultures were negative. He was put on sulfadiazine for a short time without improvement. The x-ray revealed numerous small nodules throughout both lungs and an impression of miliary tuberculosis was recorded. Two days later there was shown an increase of this process. The blood picture was not remarkable except that in the face of the sustained febrile course the white counts were as follows: 5,600, 10,800, 10,500, 14,200, 9,900. The urine examinations were negative. There was no report of sputum examination on the clinical record accompanying the patient.

On his admission to Halloran, the patient's temperature was 103° F., pulse 112, respiration 24. Blood pressure was 110/68. The patient was acutely ill and made small movements of arms and legs in a nervous manner. He was in a semi-stuporous condition a great deal of the time, although when aroused he answered questions intelligently and promptly. Physical findings were largely confined to the respiratory system. Here the examination revealed slight impairment front

and back and fine and coarse musical rales scattered throughout both lungs. The reflexes were hyperactive and no pathological reflexes were present. The spleen and liver were not palpable.

Aside from the chest x ray (Fig 51) which revealed widespread diffuse and very numerous miliary lesions of the lungs, all laboratory tests were normal except for the sedimentation rate which was 31 mm. Lumbar puncture was performed and the findings were normal. On July 19, 1944 a tubercle was seen in the right fundus. The patient continued on a downward course, the fever being maintained until his death on July 21, 1944.

The autopsy showed that the patient died of miliary tuberculosis of the lungs, spleen, liver, kidneys, adrenals and thyroid. The lungs showed extensive caseation of the miliary disease and tiny cavity formations. Special stains showed innumerable acid fast bacilli. The mediastinal lymph nodes were moderately enlarged and not caseous, but mycobacterium tuberculosis was seen on direct smear.

Summary—Although this patient exhibited many of the signs and symptoms of typhoid fever the fact that miliary disease of the lungs was discovered by x-ray early in the course of his illness established the diagnosis and the outcome was never in doubt.

COMMENT

The mildly positive Widal tests and negative tuberculin reactions in Case II confused the issue. The former did not prove that the patient had typhoid fever, the latter that he did not have tuberculosis. The fact that as the disease progressed into the third and fourth weeks the Widal test did not become more positive especially in the higher dilutions made the diagnosis of typhoid fever questionable. The agglutinations exhibited may have been nonspecific in nature or due to previous inoculations against typhoid fever.

In the light of the autopsy findings the negative tuberculin tests were obviously due to anergy caused by the overwhelming tuberculous infection.

Pathologically these three cases (one Negro, two white patients) belong to Rich and McCordock's classification of acute caseating miliary tuberculosis. The lesions were necrotic and contained myriads of tubercle bacilli. This type is the opposite of the "hard" tubercle type of miliary disease in which necrosis appears late, if ever, and tubercle bacilli are scarce in the lesions. It seems logical to assume that the sources of the dissemination of the tubercle bacilli were the Ghon tubercle in Case I, a caseated mesenteric node in Case II, and a mediastinal node in Case III, but actual proof is lacking. The bacilli were discharged in large numbers into the blood stream of a hypersensitive body thus producing caseating miliary lesions.

If one runs through the minut of signs and symptoms of typhoid fever he finds that all three patients had much in common with that disease. The illness began with malaise and anorexia and later the patients had chills and high, prolonged fever, epistaxis, bronchitis, muscle twitching, headache, delirium and relatively low blood counts. One patient had a dicrotic pulse, and an enlarged spleen. Two had abdomi-

inal distention and tympanites. One had a weakly positive Widal in the lower dilutions. None, however, had rose spots, or positive blood, urine or feces cultures for typhoid bacilli.

Possibly immediate antemortem roentgenograms of the lungs would have revealed miliary disease in Case I and II. The final films in both instances were taken five days prior to death.

One is impressed with the fact that without positive evidence of miliary disease of the lungs the diagnosis of disseminated miliary tuberculosis cannot always be made with certainty. Negative evidence is, however, strongly supportive of the diagnosis—that is, an absence of any positive laboratory tests for an etiological agent to explain the illness. The relatively low white blood count is also in favor of the diagnosis of acute disseminated miliary tuberculosis.

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TUBERCULOUS MENINGITIS WITH UNUSUAL FEATURES IN YOUNG ADULTS*

CAPTAIN HARRY L. KATZ AND CAPTAIN HAROLD A. ABEL
MEDICAL CORPS, ARMY OF THE UNITED STATES

TUBERCULOUS meningitis is principally a disease of childhood. Neal,¹ Segal,² Blacklock and Griffin,³ and Levinson,⁴ in a study of their own cases as well as those collected from the literature, indicate that in approximately 90 per cent of cases the disease occurs in the first decade of life. Meningitis accounts for death in about 65 per cent of children who succumb to tuberculosis. However, the disease can never be excluded on the basis of age, as it may appear in all age groups.

In military service, under conditions of stress and situations peculiar to the strenuous activities of military life a recrudescence of activity of latent tuberculous foci with a progression to tuberculous meningitis is not an uncommon occurrence.

The frequency of tuberculous meningitis encountered in the military service is second only to meningococcic meningitis. At Tilton General Hospital six cases of tuberculous meningitis were studied in the past year. A review of these cases indicates that tuberculous meningitis in adults is not always insidious but may be acute in its onset and fulminating in its course. The symptomatology, the physical, neurological and laboratory findings are variable and inconstant. The disease simulates and is frequently confused with encephalitis, Jacksonian epilepsy, lymphocytic meningitis, poliomyelitis, lymphatic or myelogenous leukemia, and intracranial neoplasms.

Three cases of tuberculous meningitis are presented to illustrate the variability in its clinical and laboratory manifestations, the diagnostic difficulties and the pathogenesis.

CASE I. WIDELY DISSEMINATED LYMPHOHEMATOGENOUS DISEASE CLINICALLY SIMULATING LYMPHATIC LEUKEMIA, TERMINATING IN TUBERCULOUS MENINGITIS

A 27 year old Negro soldier was admitted to an overseas general hospital on July 27, 1944 with the diagnosis of lymphatic leukemia. The patient was apparently in good health until the middle of June, at which time he noticed a slowly developing painless enlargement of the lymph nodes in the right axillary and right epitrochlear regions. There was an associated dull pain in the lower retrosternal area with radiation to both axillae and mild dyspnea. Examination at that time revealed the presence of a generalized lymphadenopathy. The lymph nodes in the left postauricular and in the left axillary regions were firm, matted

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Lt. Colonel S. Weintraub, Chief of the Laboratory Service, performed the postmortem examinations in the cases presented.

together, and not attached to the skin. The inguinal and epitrochlear nodes were discrete. Blood studies revealed red blood cells, 4,000,000, hemoglobin, 13.5 gm., and white blood cells, 18,600 with 84 per cent lymphocytes and 2 to 3 per cent lymphoblasts.

On admission to Tilton General Hospital, August 29, 1944, the patient complained of marked fatigability and weakness. He appeared emaciated and chronically ill. He stated that the lymph nodes had increased in size since the onset of illness and had become painful, especially in the cervical and axillary regions.

Physical examination revealed petechial hemorrhages in the skin, conjunctivae and mucous membranes. The gums were edematous, spongy and bled easily. A large hemorrhagic area was present on the soft palate and the left tonsil. Examination of the heart showed the presence of a soft systolic murmur of low intensity. The lungs were normal to percussion and auscultation. A tender mass of matted lymph nodes was present in the left submandibular, left cervical, and left axillary regions, part of a generalized lymphadenopathy. The liver and spleen were palpable one and three fingerbreadths below the costal margins respectively. Chest x-ray showed normal parenchymal and cardiac structures. The laboratory findings on admission were blood smears, negative for malarial parasites, Kahn test, negative, blood cultures, negative for aerobic and anaerobic or

TABLE 1 —HEMATOLOGICAL FINDINGS IN CASE I

Date	Red Blood Cells ($\times 1000$)	Hemoglobin, Per Cent	White Blood Cells	Polymorphonuclears, Per Cent	Lymphocytes, Per Cent
August 30	2,040	55	43,000	3	97
September 9	0,940	20	80,000	1	99
September 21	0,900	20	12,400	4	96
October 20	2,150	50	9,500	10	90
November 19	3,430	70	4,700	15	85
December 2	4,060	76	2,800	74	11
December 12	4,400	78	3,650	52	46

ganisms, red blood cells, 2,000,000 with a moderate degree of anisocytosis, macrocytosis, and hypochromasia, hemoglobin, 55 per cent, and white blood cells, 43,000 with 97 per cent lymphocytes.

The patient's course in the hospital was characterized by septic temperature with elevation to 103°–104° F. The red blood cell count decreased rapidly to levels below 1,000,000. He had persistent epistaxis, bleeding from gums and mucosal surfaces. He was transfused on six occasions in amounts varying from 500 to 1000 cc of citrated blood. Treatment with parenteral penicillin solution to a total dosage of 800,000 units was instituted in the hope of controlling infection. However, this was without therapeutic benefit. In mid-October the patient's blood picture began to show spontaneous improvement. Although blood transfusions were discontinued, the red blood cell count increased to 4,200,000 and the white blood cells decreased to 3550 with 11 per cent lymphocytes. The white cell count varied from 3000 to 5000 during the latter part of his illness. This spontaneous hematological improvement was considered unusual in the face of a progressive decline in his general condition as manifested by progressive emaciation and persistent septic temperature. Coincident with the improvement in the blood picture, the spleen and lymph nodes regressed somewhat in size, and spontaneous nasal and mucous membrane bleeding ceased. Table 1 shows the hematological changes during the course of the patient's illness.

On October 13 the patient developed signs of a right pleural effusion and a pericardial friction rub. Chest x-ray, revealed a moderate homogeneous density over the right chest and a widening of the cardiac silhouette suggestive of a right pleural and pericardial effusion. On December 18 a thoracentesis was performed and 200 cc. of clear, straw-colored fluid was aspirated, showing a specific gravity of 1.020, a cell count of 500 with 90 per cent lymphocytes, and protein content of 64 mg per 100 cc.

The patient's condition progressively declined and on January 12, 1945 he had a generalized clonic convulsion followed by the development of evanescent

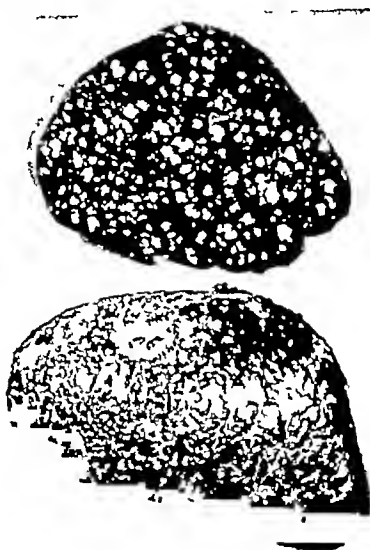


Fig 52—External and sagittal section of spleen. There is a diffuse involvement of the parenchyma with miliary and nodular caseous foci of varying size.

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POSTMORTEM EXAMINATION—The essential findings were as follows. The peritoneal cavity contained about 300 cc. of cloudy yellowish fluid. The omentum was studded with numerous caseous tubercles of varying size. The right pleural cavity was obliterated and the left pleural space contained 200 cc. of clear yellowish fluid. The pericardial surface, particularly in the region of the left ventricle, was covered by a fine fibrinous exudate. The liver, spleen and diaphragm were studded with miliary tubercles 1 to 2 mm in diameter and numerous

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Fig 52—External and sagittal section of spleen. There is a diffuse involvement of the parenchyma with miliary and nodular caseous foci of varying size.

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POSTMORTEM EXAMINATION.—The essential findings were as follows. The peritoneal cavity contained about 300 cc. of cloudy yellowish fluid. The omentum was studded with numerous caseous tubercles of varying size. The right pleural cavity was obliterated and the left pleural space contained 200 cc. of clear yellowish fluid. The pericardial surface, particularly in the region of the left ventricle, was covered by a fine fibrinous exudate. The liver, spleen and diaphragm were studded with miliary tubercles 1 to 2 mm in diameter and numerous

nodules with caseous centers The cut surfaces of the spleen, liver, kidneys and diaphragm showed a diffuse involvement of the entire parenchyma with caseous nodules of varying size and anatomic age (Figs 52 and 53) The tracheobronchial, parapancreatic and omental lymph nodes revealed a diffuse caseous nodular involvement The center of many of these nodules contained necrotic, yellowish, cheesy material The severity of involvement was most marked in the tracheobronchial lymph nodes The brain showed a flattening of the external surface and a dilatation of the pial vessels The base of the brain including the cerebral peduncles, the pons, the circle of Willis, the optic chiasm, the superior surface

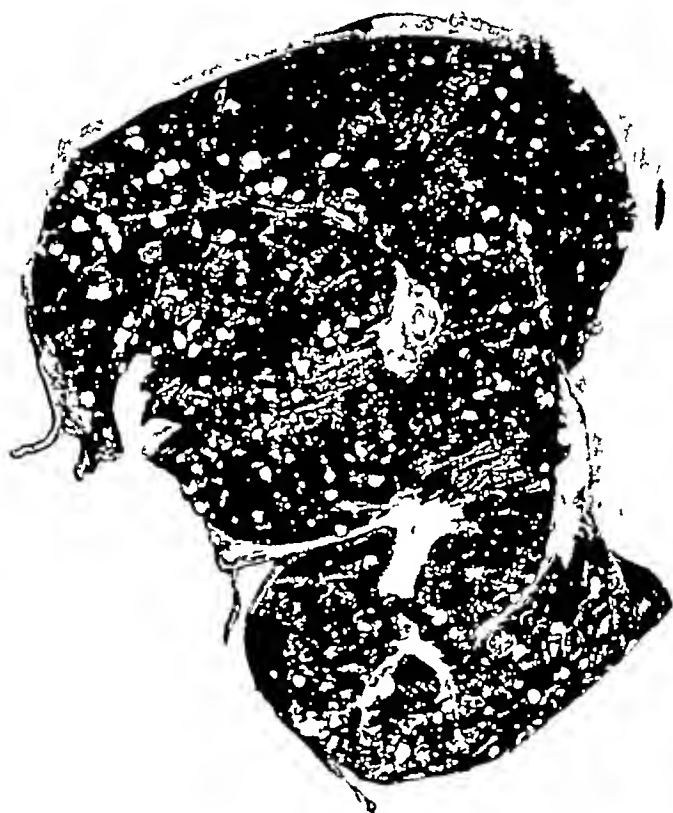


Fig 53.—Sagittal section of liver There is a diffuse involvement of the parenchyma with miliary and nodular caseous foci Many of the larger foci have necrotic centers

of the cerebellum and the pituitary was covered by soft, yellowish necrotic exudate Miliary tubercles of recent origin were scattered through the superficial surface of the base of the brain

Examination of the lungs revealed the presence of small encapsulated caseous and calcified foci in the left lower lobe Miliary foci were scattered through all the lobes of the lung The bone marrow of the sternum ribs and femur appeared hyperplastic

Final anatomic diagnosis 1 Tuberculous meningitis 2 Tuberculous caseous lymphadenitis of the paratracheal, tracheobronchial, peribronchial, parapancreatic mesenteric mesocolic, omental and paravertebral lymph nodes 3 Nodular ca-

seous tuberculosis of liver spleen, kidneys and diaphragm 4 Encapsulated caseous tuberculous foci all lobes of lung 5 Miliary tuberculous foci of liver spleen kidneys, lung diaphragm and brain 6 Encapsulated calcified primary complex in left lower lobe. 7 Tuberculous fibrinous peritonitis 8 Tuberculous fibrinous pericarditis. 9 Tuberculous fibrinous pleuritis left and loculated hydrothorax right

Comment.—This case with widely disseminated lymphohematogenous tuberculosis terminating in tuberculous meningitis clinically simulated lymphatic leukemia. The question arose whether the patient was a victim of two distinct diseases, i.e. lymphatic leukemia and disseminated tuberculosis, or whether the leukemic blood picture was the result of a tuberculous infection affecting the lymphohemopoietic system. On autopsy leukemic infiltrations were not evident in any of the organs. The blood dyscrasia was therefore characterized by a lymphocytic leukemoid reaction in response to the widely disseminated tuberculous infection. This is further substantiated by the reversal of the hematological findings to essentially normal levels during the last few weeks of the patient's life. The generalized hyperplasia of the lymph nodes associated with a toxic depression of the bone marrow resulted in a reactive absolute and relative lymphocytosis.

This case also presents evidence of progression of the lymph node component of the primary complex with anatomic healing of the primary pulmonary focus. This reaction is usually seen in young Negro adults. The reaction is not the usual one seen in the primary or reinfection type of tuberculosis. It differs from the primary in that the pulmonary component is not concomitantly involved with the hilar lymph node component. It differs from the reinfection type in that the organs involved do not show such extensive caseous nodular disseminations and the lymph nodes are not the site of progressive tuberculous involvement.

CASE II TUBERCULOUS MENINGITIS WITH INITIAL SYMPTOMS SUGGESTIVE OF POSTPNEUMONIC PLEURAL EFFUSION THE MENINGEAL SYMPTOMS SIMULATING JACKSONIAN EPILEPSY

A 24 year old male Negro was admitted to Tilton General Hospital on April 8, 1945 as a transfer from an overseas medical installation with a diagnosis of postpneumonic serofibrinous pleurisy left thorax. He was apparently in good health until the beginning of January 1945 at which time he developed a moderate cough, muscular aches, sensation of chilliness, feverish feeling and left chest pain. The diagnosis of bronchopneumonia was made and he was treated with sulfadiazine (total 60 gm.) and parenteral penicillin (total 900,000 units) without apparent benefit. On January 13 chest x ray revealed the presence of a left hydrothorax. Thoracenteses were performed on January 13 and January 23. Straw-colored serofibrinous fluid was aspirated in amounts varying from 1000 to 2000 cc. For several weeks his temperature was septic in type with elevation to 101 F. The temperature gradually subsided and the patient showed progressive symptomatic improvement.

On admission to Tilton General Hospital, his temperature was normal and condition excellent. Examination of the chest revealed a moderate limitation of motion of the left thorax, impaired resonance to percussion and moderate sup-

pression of breath sounds in the region of the left lower lobe Chest x-ray (April 10, 1945) showed a homogeneous density extending upward along the lateral thoracic region to the level of the fourth rib anteriorly

Laboratory studies were as follows blood and urine, normal, Kahn, negative, sedimentation rate, 30 mm per hour Chest fluid (April 16, 1945) leukocytes 12,100 with 96 per cent lymphocytes, protein content, 51 mg per 100 cc, sugar content, 40 mg per 100 cc, specific gravity 1.022, and smear for acid-fast bacilli, negative

The patient's condition progressed uneventfully until April 11, when a low grade temperature with gradual elevation to 101° F was noted He also began to complain of persistent frontal headaches and intermittent vomiting The next day he suddenly developed a typical grand mal attack manifested by a generalized clonic convulsion, temporary loss of consciousness and rolling movements of both eyes This episode lasted for about 3 minutes Recovery was without demonstrable neurological or mental sequelae He had three similar attacks within a period of ten days Spinal fluid findings (April 17, 1945) were essentially normal Skull x-ray was normal Electroencephalographic tracing revealed a pace irregularity with frequent occurrence of four to five large waves per second This finding was consistent with the diagnosis of epilepsy or a related disorder

TABLE 2—CEREBROSPINAL FLUID FINDINGS IN CASE II

Date	Appearance	Pressure, Cm. Water	Cell Count	Lymphocytes, Per Cent	Sugar, Mg per 100 Cc	Protein, Mg per 100 Cc	Chlorides, Mg per 100 Cc	Levinson Test	Tryptophan	Smear for Bacillus of Tuberculosis	Range Test
4/17/45	Clear	20	3	100	57	140	714			Neg	000000000
4/26/45	Clear	35	30	100	40	140	650	Neg	Neg	Neg	001234400
5/1/45	Clear	51	62	54	32	200	600	Pos	Pos	Neg	111345400

A repeat electroencephalographic tracing with right frontal localization showed an out-of-phase activity localized to the anterior region of the frontal lobe, and all leads showed a high voltage of slow activity

On April 27 the patient developed a twitch of the left facial muscles, fibrillary movements of the left upper eyelid, and evanescent nuchal rigidity Neurological examination at that time revealed hyperactive deep reflexes on the right side and in absence of all superficial reflexes These neurological findings were transitory but became constant three days later Babinski, Brudzinski and Kernig signs became positive on the right Spinal punctures were performed on three occasions during the latter part of his illness Table 2 indicates the changes in the cerebrospinal fluid with the progression of the disease The patient's condition progressively declined He began to manifest increasing mental deterioration, stuttering speech, left facial palsy, diplopia, followed by ophthalmoplegia, right hemiplegia and loss of consciousness He expired on May 4, 1945, five months after the onset of the pleural effusion

POSTMORTEM EXAMINATION—The loops of the intestines were moderately distended and adherent to one another by fine fibrinous adhesions The serosal surface of the small and large intestine was covered in areas by a granular fibrinous exudate About 10 cm proximal to the ileocecal valve there was a punched-out shallow ulcer with undetermined edges, 3 cm in diameter In sep-

among the intestinal loops several small areas of intussusception were encountered. The mesenteric lymph nodes were slightly enlarged and contained caseous foci. The parietal peritoneum as well as its reflection on the undersurface of the diaphragm, and the superior surface of the liver were studded with milium and caseous tuberculous foci of varying size and stages of development.

The right pleural cavity contained approximately 200 cc. of brownish fluid. The left pleura was thickened by fibrinous deposits and the left pleural space was obliterated. The diaphragmatic pleura was studded with milium and caseous foci. The tracheobronchial lymph nodes were enlarged matted together and on section contained large caseous foci replacing the entire lymph node tissue in areas. Several small encapsulated calcified foci were present in both lobes of the left lung and in one paratracheal lymph node.

The brain showed the presence of a grayish fibropurulent membrane covering the left frontal parietal lobes, particularly in the region of the motor area. A smear taken from this exudate revealed numerous acid fast bacilli. The base of the brain was normal in appearance.

Final anatomic diagnosis: 1 Tuberculous meningitis. 2 Caseous tuberculosis of the tracheobronchial lymph nodes. 3 Primary complex, multiple encapsulated calcified foci, left lung. 4 Fibrinous peritonitis, generalized tuberculous. 5 Intussusception, multiple, small intestine secondary to tuberculous peritonitis. 6 Tuberculous ulcer of ileum. 7 Tuberculous pleuritis, fibrinous left and tuberculous effusion, right.

Comment.—This case presents a disseminated tuberculosis involving the pleural surfaces, peritoneum, diaphragm and meninges. A reactivation of an old primary tuberculous focus in the tracheobronchial lymph nodes with caseous involvement served as a source of the metastatic spread. The presence of encapsulated calcified foci in the left lung and in the center of a paratracheal lymph node indicated the relative antiquity of the primary infection. The development of the pleuritis, peritonitis and meningitis in this case was due to repeated lymphohematogenous dissemination of tubercle bacilli from the caseous tracheobronchial lymph nodes.

The disease was initiated by symptoms suggestive of a bronchopneumonia soon followed by a pleural effusion. This case emphasizes that pleural effusions must be considered of tuberculous etiology until proved otherwise. The so-called postpneumonic serofibrinous pleural effusion should be regarded with suspicion. The failure to find tubercle bacilli in the pleural or spinal fluid should not deter the examiner from considering the fluid tuberculous.

The serial spinal fluid studies indicate that the chemical and cytological aberrations are late manifestations in the disease. It is of interest that the spinal fluid findings were normal at the time of onset of the initial meningeal symptoms. The sugar and chloride content decreased with the progression of the disease. The Levinson, tryptophan and Lange tests become positive only in the terminal phase.

The localization of the meningeal exudate to the left frontal and parietal lobes accounted for the focalization of the neurological signs to the right side of the body, and for the electroencephalographic pattern simulating Jacksonian epilepsy.

CASE III GENITOURINARY TUBERCULOSIS WITH EVENTUAL HEMATOGENOUS SPREAD TO THE MENINGES

A 38 year old white man was admitted to Tilton General Hospital on February 11, 1945, with increasingly severe headaches, muscular aches, feverish feeling, and stiffness of the neck of four days' duration. In September, 1942 he had an acute episode of right epididymitis which promptly subsided on conservative therapy. In December, 1944 he had a recurrence of the epididymitis at which time he was hospitalized for twenty-two days. Studies to rule out tuberculous etiology included urine culture for tubercle bacilli and intravenous pyelography. The results did not indicate the presence of a tuberculous infection and the patient was discharged with the diagnosis of acute nonvenereal, nonsuppurative, right epididymitis. At the time of discharge he was essentially asymptomatic, however, residual thickening of the right epididymis was present. Two weeks later, he began having intermittent frontal headaches lasting two to three hours. Several days later this became associated with sensation of chilliness, diaphoresis, lacrimation of the right eye, and feverish feeling.

Examination revealed a white male, appearing chronically ill. Moderate nuchal rigidity was present. Examination of the heart and lungs did not reveal any abnormal findings. A small mass, the size of a hazelnut, was palpable in the lower pole of the right testis. The right epididymis appeared hard, firm and cordlike. The left lobe of the prostate was tender and nodular on palpation. Neurological examination was normal with the exception of generalized hyperactive deep reflexes.

Laboratory studies revealed normal total and differential blood counts. Blood smears were negative for malarial parasites. Spinal fluid (February 12, 1945) findings were 2 white blood cells per cubic millimeter, sugar, 40.8 mg per 100 cc and total protein, 60 mg per 100 cc. Chest x-ray showed a fibrotic type of infiltration of minimal extent in the left first intercostal space suggestive of a healed tuberculous focus.

The patient's temperature fluctuated from 100° to 102° F. On the third day of hospitalization he became disoriented, delirious, and tended to lapse into periods of semiconsciousness. The nuchal rigidity became more marked and deep reflexes became markedly hyperactive. Positive Chaddock, Hoffman, Kernig and Brudzinski reflexes were elicited bilaterally. The next day right ankle clonus was present and there was a loss of all superficial reflexes. Lumbar puncture was repeated on February 14, with the following cerebrospinal fluid findings: pressure, 30 cm of water, cells, 5 polynuclears per cubic millimeter, sugar 31 mg, protein 293 mg and chlorides 424 mg per 100 cc, smear negative for acid-fast bacilli.

Though the diagnosis of tuberculous meningitis was entertained, the patient was treated with penicillin solution receiving 20,000 units every three hours intramuscularly for four days without evident beneficial effect. He deteriorated steadily, developing left facial paralysis, paresis of the muscles of deglutition, increasing lethargy and finally coma. Cheyne-Stokes respiration developed on February 18 followed by signs of pulmonary edema. He expired on February 19, eight days after admission.

POSTMORTEM EXAMINATION—Pulmonary System A small encapsulated partially calcified focus was present in the right middle lobe. There were multiple similar foci of varying size in the peribronchial lymph nodes. A few of these foci contained caseous centers, others were totally calcified and an occasional focus contained caseous structures. Present in the right upper lobe was a circumscribed caseous nodule about 1 cm in diameter with a central area of rarefaction. Hemorrhagic edema was evident in both lower lobes.

The spleen and liver contained an occasional well circumscribed small nodule measuring a half to one cm in diameter.

Genitourinary Tract The prostate was enlarged and firm. The right lobe of the prostate was almost completely replaced by a large tuberculous caseous nodule. The periprostatic lymph nodes contained many caseous foci of varying size and age. The seminal vesicles were indurated and in areas replaced by nodular tuberculous foci. The right epididymis was markedly enlarged and almost replaced in toto by large caseous nodules.

Central Nervous System The sulci were narrowed and the convolutions flattened. The meninges over the base of the brain appeared markedly edematous. A thin fibrinous deposit was present in the region of the optic chiasm, over the lateral foramen and extended to involve the olfactory bulbs, tracts, the medulla pons and cerebellum. The lateral ventricles were moderately dilated and the lateral foramina were partially obstructed.

Final Anatomic Diagnosis 1 Tuberculous meningitis and hydrocephalus. 2 Encapsulated, caseous, calcified tuberculous foci in right middle lobe, tracheo-bronchial lymph nodes, spleen and liver. 3 Circumscribed caseous tuberculous focus in right upper lobe (inspissated excavation). 4 Caseo-ulcerative tuberculous of the prostate, seminal vesicles and right epididymis. 5 Nodular caseous tuberculosis of the periprostatic and inguinal lymph nodes.

Comment—This case presents genitourinary organ tuberculosis with hematogenous spread to the meninges resulting in tuberculous meningitis and hydrocephalus. This case well illustrates that extrapulmonary tuberculosis is a nidus of grave events which requires early diagnosis and prompt eradication. It is conceivable that the repeated episodes of acute epididymitis which started in 1942 and for which the patient was hospitalized in 1944 were tuberculous in etiology. Had the diagnosis been properly made at that time the dissemination might have been prevented. The sequence of events in this case illustrates that tuberculous meningitis may be acute rather than insidious in onset and fulminating in course. The entire course in this patient was only twelve days from the time of onset of the first sign of meningeal involvement. The spinal fluid findings indicate that neither the cell count nor the percentage of lymphocytes is diagnostic of tuberculous meningitis.

The pathology in the left lung is the type generally considered to be of the chronic form of pulmonary tuberculosis as evidenced by the typical location of the original cavity. Its evident chronicity is manifested by encapsulation and inspissation. Pathological findings indicate repeated hematogenous dissemination. Tuberculous foci of all ages were present in the lungs, liver, spleen and lymph nodes varying from acute exudative to chronic productive in character.

REMARKS

The pathogenesis of tuberculous meningitis is controversial. Rich and McCordock⁵ believe that the origin of acute exudative meningitis depends upon the presence of localized caseous foci which discharge bacilli into the subarachnoid space. Thus the development of meningitis is an accidental event, the result of infection from a focus most frequently located in the substance of the brain in close proximity to the meninges or ventricles. The sequence of events leading to menin-

gitis as advanced by these authors is as follows: the dissemination of bacilli from a primary tuberculous lesion, usually in childhood, productive of caseous foci in the viscera and in structures adjacent to the meninges, and the discharge of bacilli from these localized foci into the meninges or ventricles. Walker⁶ and MacGregor and Green⁷ are in agreement with this view of pathogenesis.

However, the frequent association of generalized miliary tuberculosis with meningitis has led to the view that tuberculous meningitis is part of a generalized hematogenous dissemination. Ragins,⁸ in an anatomical study of cases with tuberculous meningitis, was unable to demonstrate the presence of a localized tuberculoma in 82 per cent of his cases. Beres and Meltzer,⁹ in a similar study of twenty-eight cases, found twenty-two of hematogenous origin and in only six cases were tuberculous lesions in the cerebral substance found. In these six cases the authors were unable to state whether the localized foci were the result or the cause of the meningeal process.

In the three cases presented, the pathogenesis of the meningitis is attributable to repeated hematogenous dissemination from the thoracic lymph nodes in the first two cases and from the genitourinary tract in the third case. Tuberculomas within the substance of the brain adjacent to the meninges or ventricles were not demonstrated. The tuberculous foci within the brain substance and those adjacent to the inflammatory meningeal exudate were of the same anatomic age as the tuberculous foci in the other viscera. Consequently, they are considered to be part of the generalized dissemination rather than the precursors of meningitis.

The myeloid type of leukemoid blood picture occurs in a wide range of clinical conditions. Nanta,¹⁰ in a study of thirty-one cases in the literature, concluded that tuberculosis could produce a diffuse myeloid hyperplasia and reproduce the myeloleukemoid blood picture. Marzullo and de Veer,¹¹ and Custer and Crocker¹² each presented two cases of tuberculous infection with a myeloleukemoid blood picture and a clinical course simulating acute myelogenous leukemia. The histological examination of the tissues in each case was negative for leukemic infiltration in the various organs. The tuberculous process in each case was similar and was manifested by an acute, widespread and massive caseation primarily of the lymph nodes. The finding of a lymphatic leukemoid reaction in association with widely disseminated tuberculosis of the lymph nodes is rare and unusual.

The type of tuberculosis found in the first two cases has been classified by Aschoff¹² as "puberty tuberculosis." It is characterized by massive caseation with relative confinement to the hilar lymph nodes. The characteristic feature of this disease is the liability to lymphohematogenous dissemination of the tubercle bacillus with widespread organ involvement and usual termination in tuberculous meningitis.

SUMMARY AND CONCLUSIONS

1 The frequency of tuberculous meningitis in the military service is second only to meningococcic meningitis

2 The clinical course, laboratory and physical findings in the cases presented are variable and inconstant. The spinal fluid aberrations are late manifestations in the disease

3 Three cases of tuberculous meningitis in young adults are presented. The first case with widely disseminated lymphohematogenous disease clinically simulated lymphatic leukemia. The second case manifested initial symptoms suggestive of a postpneumonic pleural effusion. The meningeal symptoms simulated Jacksonian epilepsy as evidenced by clinical and electroencephalographic findings. The third case had recurrent episodes of epididymitis for approximately three years with eventual termination in tuberculous meningitis

4 The pathological picture in the first two cases is one of a diffuse hematogenous and lymphatic dissemination of nodular caseous foci from caseous hilar lymph glands. The third case showed extensive caseo-ulcerative tuberculosis of the prostate, seminal vesicles and right epididymis, with caseous involvement of the periprostatic and inguinal lymph nodes.

5 The pathogenesis of the meningitis in these cases is attributed to repeated hematogenous dissemination of tubercle bacilli to the meninges, and is considered to be part of a generalized hematogenous dissemination. Tuberculomas adjacent to the meninges or ventricles were not demonstrated in these cases

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THIOURACIL THERAPY IN THE PREOPERATIVE PREPARATION OF THYROTOXIC PATIENTS

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VARIOUS means have been employed to prepare the thyrotoxic patient for thyroidectomy, the aim being to lower the metabolic rate to as nearly normal as possible, to produce a remission of symptoms and to secure a gain in weight.

Physical and chemical agents have been employed to correct the physiological abnormality. Bed rest and adequate sedation have been employed but the results have been minimal. In 1923 Plummer¹ introduced the use of iodine in the form of Lugol's solution for the preoperative treatment of the thyrotoxic patient. There was a resultant decrease in the mortality and morbidity following this treatment but the problem was not solved. The metabolism did not always return to normal. Some patients remained moderately thyrotoxic and some remained resistant to iodine. With the advent of thiouracil thyrotoxicosis has been controlled during the active stage producing a remission of symptoms, gains in weight and better subjects for surgery. Indeed, some workers feel that the medical treatment of hyperthyroidism with thiouracil will eventually replace surgery.

It had been known before the discovery of thiouracil that some substances when fed to animals would produce goiter. Chesney² fed rabbits a cabbage diet and these animals developed huge goiters. Enlargement of the thyroid gland was produced in animals to whom thiocyanate was administered, while the administration of iodine abolished this type of goiter.³ Kennedy and Purves⁴ fed rats a diet of brassica (rape) seeds and produced goiters with hyperplasia of the epithelium and loss of colloid. Iodine feeding had not affected the hyperplasia but the administration of thyroid extract or hypophysectomy could abolish the hyperplasia. Allylthiourea produced the same changes as reported by Kennedy.⁵ MacKenzie and MacKenzie⁶ found that sulfonamides and thiourea compounds produced lowering of the basal metabolic rate and enlargement of the gland with loss of colloid. Administration of thyroxin would abolish the effects on the thyroid glands as would hypophysectomy, but iodine had no effect. Richter and Clusby⁷ made similar observations using thiocarbamide. Astwood⁸ tested 106 compounds which inhibited the function of the thyroid gland, to compare their activity and toxicity. He determined that 2-thiouracil was among the most effective and that unlike goitrogens of the thiocyanate group the hyperplastic effect of the gland was not

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abolished by the coincident administrations of iodine Astwood⁹ first tried thiourea and later thiouracil for the treatment of three thyrotoxic patients

Williams and Bissell¹⁰ reported nine cases treated with thiouracil with a subsequent fall in their basal metabolic rate to normal Williams and Clute¹¹ reported treatment of fifty cases with thiouracil In most cases, the basal metabolic rate became normal and toxic manifestations of disease disappeared Clute and Williams¹² reported thirty cases operated upon after thiouracil treatment They reported a reduction of the basal metabolic rate to normal with a corresponding decrease in the symptoms of the disease in almost all cases Postoperative courses of the patients were reasonably smooth and uneventful Williams and Clute¹³ reported 152 additional cases and confirmed their previous results

Newman¹⁴ prepared a series of thirty-four patients with thyrotoxicosis for operation with thiouracil, the first six patients treated with thiouracil alone were found at operation to have very vascular friable thyroid glands The remainder of the patients were given iodine and thiouracil simultaneously In the latter the glands were found generally firmer, less vascular and easier, technically, to remove Excellent results were obtained preoperatively and postoperatively Moore and his associates¹⁵ treated fifty-three thyrotoxic patients with thiouracil preoperatively They reported thiouracil as superior to iodine as a preparation for thyroidectomy because regardless of the degree of elevation of the metabolic rate prior to therapy, the patients came to operations with normal basal metabolic rates They noted the increased vascularity of the gland with its concomitant operative difficulties Bartels¹⁶ ¹⁷ reported 100 cases with excellent results Further reference to this series will be noted later Reveno,¹⁸ in a survey of thirty-two cases treated with 0.6 gm daily, in three doses of 0.2 gm each, concluded that thiouracil appeared to be the agent of choice in inducing and maintaining a state of remission in thyrotoxicosis

Palmer,¹⁹ in a series of fifty cases treated with thiouracil, encountered no serious complications during a period extending from one to ten months, no instance of drug intolerance, idiosyncrasy or refractoriness was noted The only serious effect was a leukopenia which was transient No patient failed to respond to the drug Over one half of the fifty patients had received 0.065 gm of desiccated thyroid to 0.8 mg of thyroxin daily, the dose being dependent on the degree of exophthalmos present In no case did the thiouracil effect appear to be inhibited by giving thyroid substance No patients required operation

METHOD OF STUDY IN OUR SERIES

The cases included in our series were of soldiers who developed symptoms of thyrotoxicosis while on active duty in the armed forces

They were all stationed in the same service command and were transferred to our hospital for specialized treatment. All patients in this series were those who, prior to the onset of the symptoms of thyrotoxicosis, were found upon physical examination to be qualified for full military duty under the provisions of existing Army regulation MR 19. The minimum length of service in the Army had been eight months. The maximum had been four and one-half years before thyrotoxic symptoms appeared.

Plan of Treatment—A definite plan of treatment was outlined. Every effort was made to profit by the experiences of others who had reported their results with thyrotoxic patients treated with thiouracil. Bartels^{16, 17} reported that technical difficulties at operation occurred in patients treated only with thiouracil. Thiouracil produced a hyperplastic but nonfunctioning goiter. This hyperplasia was accompanied by an increased vascularity and friability which made the gland more difficult to handle and hemostasis was difficult. The bleeding of the entire site was so extensive that there was difficulty in isolating the parathyroid glands and the recurrent laryngeal nerve. He overcame this difficulty by administering Lugol's solution along with thiouracil. Iodine was given daily during the three weeks preoperative period and the thiouracil was discontinued one week before operation. The iodine given preoperatively produced a firmness of the gland and it is possible that it played a role in reducing hyperplasia and vascularity. Bearing this in mind, we treated no patient in our series preoperatively with thiouracil only. Lugol's solution was administered for ten days prior to operation after thiouracil had reduced the basal metabolic rate to or near normal. When all symptoms of toxicity had disappeared and the patient had gained weight, the thiouracil was discontinued and the Lugol's solution given in dosage of ten minims three times a day for ten days.

Some means or agent for preventing the most serious toxic effect following thiouracil therapy, agranulocytosis, was sought. Goldsmith²¹ had found that the neutrophilic leukopenia obtained by feeding thiouracil to rats could be prevented by simultaneously feeding a solubilized liver preparation. It had been noted that the toxic reactions resulting from thiouracil were similar to those complicating sulfonamide therapy. Sebrell²⁰ has reported results on the prevention of experimental agranulocytosis in rats given sulfonamides by the administration of liver preparations. Wishing to ascertain the role liver extract played in the prevention of agranulocytosis, we gave liver extract in crude form on alternate days to a group of patients while thiouracil was administered.

Age Race Previous Treatment—The range in age was from 19 to 45 years. Two were women—members of the Women's Army Corps. One patient was an Italian prisoner of war. Twelve were Hebrews—more than 50 per cent of the group. No satisfactory explanation could

be found for this proportion. No patient had received previous treatment, which was to be expected, for an individual with a history of thyrotoxicosis would have been rejected for military service.

Classification of Patients—The cases were divided into three groups

Group I—Eight cases were included in this group. These patients were treated with thiouracil, 0.2 gm * three times a day until optimum preoperative conditions were obtained, namely, all symptoms of toxicity had disappeared and the basal metabolic rate was normal or approaching normal. Patients in this group were then given Lugol's solution, 10 minims three times a day for a period of ten days. At the end of ten days, patients were transferred to the Surgical Service. Liver extract was *not* given to this group. One patient in the group, because of a laryngeal complication, was continued on Lugol's solution beyond the ten day period.

Group II—Ten cases were included in this group. The same procedure was followed as in Group I but in addition each case received crude liver extract 1 cc intramuscularly on alternate days during the preoperative period. This was to determine the effect, if any, of liver extract in preventing changes in the hemogram due to thiouracil.

Group III—This was a control group of five patients. Lugol's solution only was given to this group. At no time did any patient in the group receive thiouracil or liver extract.

Patients were not selected for any individual group. No criteria were applied other than that the patient must be thyrotoxic. All groups were carefully observed during the preoperative and postoperative periods. A close liaison was maintained between the Medical and Surgical Services.

Clinical and Laboratory Studies—Basal metabolic rates were obtained preliminary to treatment in all groups. During the treatment, basal metabolic rates were obtained three times a week. Blood counts—white cell and differential—were made on alternate days. When the white cell count fell to 4000 or neutrophils showed a fall to 40 per cent, daily blood counts were made. When the white cell count was as low as 3500 or the differential count showed a fall of neutrophils to 30 per cent, thiouracil was discontinued. Blood cholesterol determinations were made three times a week, chest x-rays and electrocardiograms were made on admission, at operation and postoperatively, and ear, nose and throat studies, including laryngoscopy and the eye, were made with appropriate consultation at similar intervals.

The progress of the patient was observed and recorded as follows: his appearance (i.e., nervousness, restlessness, perspiration, tremor), eye signs, changes in goiter, character and rate of the pulse, blood pressure, weight, heart findings, quadriceps weakness.

Supplementary Treatment—All patients were given

1. *Complete bed rest* except for latrine privileges (latrine adjoins patient's room) and wheel-chair transportation to laboratory for elec-

* The thiouracil (Deracil) was supplied by the Lederle Laboratories, Inc., Pearl River, New York.

trocadiogram and basal metabolic rate (The laboratory for these facilities is located on the same floor as the patient's ward)

2 A diet consisting of carbohydrate 400 gm, protein 80 gm, and fat 120 gm. This was the *minimum* daily diet. The patient was encouraged to eat as much as he wished, part of the intake being in interval feedings, such as fruit juices, milk, chocolate milk, crackers, sandwiches, fruits between meals and at bedtime

3 In *tense, restless cases* phenobarbital, 0.1 gm, was administered. For sleep secenal, 0.1 gm or nembutal, 0.1 gm was given at bedtime. Nembutal, 0.1 gm at bedtime, was routinely administered the night before the basal metabolic rate determination

4 *Vitamins* All groups received a form of vitamin B complex—Triasyn B was administered in dosage of two tablets three times daily to supplement the diet. Thiamine hydrochloride in dosage of 10 mg three times daily and one vitamin A and D capsule three times daily were also administered

Anesthesia—The patients were given morphine sulfate and scopolamine in the ratio of 1 to 25 one hour and fifteen minutes prior to the induction of the anesthetic. Usually a sedative was given the night before the operation

The induction of anesthesia was accomplished with nitrous oxide and oxygen, while for its maintenance oxygen and ether were employed. An endotracheal tube was used

Spinal anesthesia²² was used in addition during operation on one of our patients to control the sympathetic overactivity due to the hyperthyroidism. The technic described by Knight²² was followed. During the preoperative treatment with thiouracil this patient developed agranulocytosis. The thiouracil had been discontinued three days prior to the onset of the agranulocytosis. This case will be reported in complete detail in a later paper

REPORT OF CASES

Group I

CASE 1—A 20 year old soldier

Family History Father has been operated upon for stomach ulcers otherwise noncontributory. *Previous Personal History* Negative. *Present Illness* The patient was admitted to a general hospital overseas in the early summer of 1944 for a three day fever which was probably dengue. At this time, a diagnosis of exophthalmic goiter was established and he was evacuated to the United States. He had noted that for three months prior to that acute febrile illness, he had been getting more nervous and restless, had been perspiring to an increasing degree and had been noticing an increasing intolerance to heat. During the past six months these symptoms had all markedly increased in degree. He had lost 25 pounds in weight despite an increased appetite and now perspired profusely most of the time. He had noted "popping" of his right eye in the past three months during which time an enlargement in his neck had also become noticeable. Palpitation and tachycardia with a precordial aching oftentimes during rest but more often precipitated by exertion, had become increasingly frequent and

troublesome during the past three months. Restlessness with insomnia had become severe. From time to time he had three or four loose bowel movements per day.

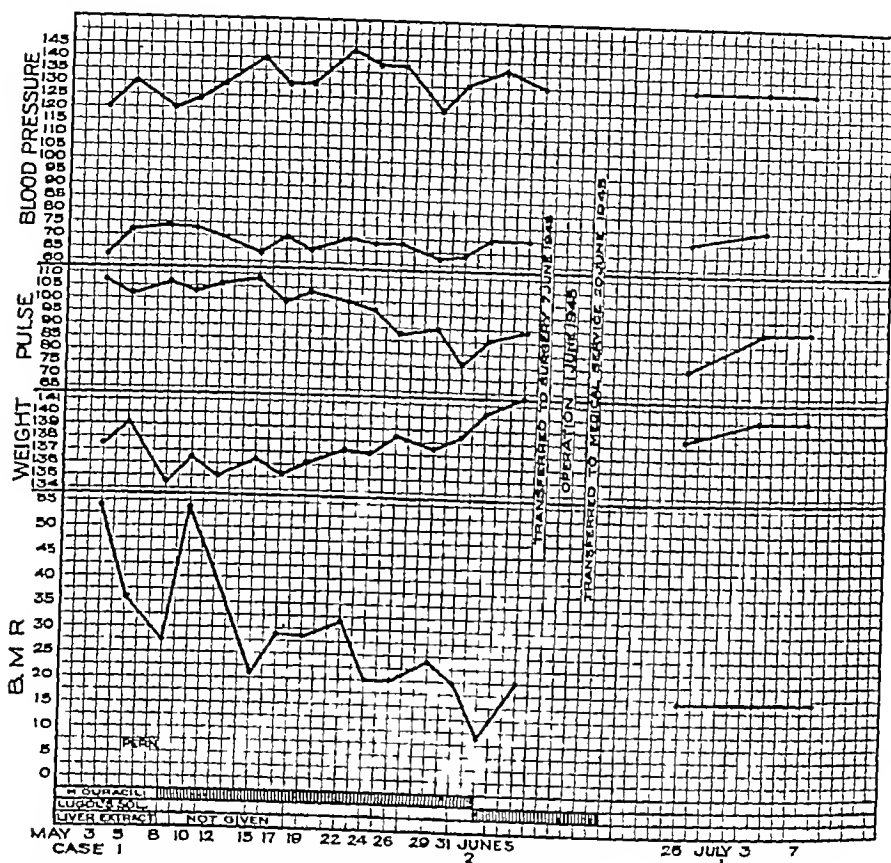


Fig 54—Course of the blood pressure, pulse, weight and basal metabolic rate in Case 1. On May 3, 1945 the basal metabolic rate was +54, weight was 133 pounds, pulse 108, blood pressure 120/64 mm Hg. Thiouracil therapy was begun on May 8 in doses 0.2 gm three times a day and continued until June 2 at which time the basal metabolic rate had dropped to +7, pulse to 85, weight had increased to 139 pounds, and the blood pressure was recorded as 130/70 mm Hg. Lugol's solution in doses of 10 minims three times a day was then administered from June 2 until June 12. The basal metabolic rate rose during this period to +20, but weight increased to 145 pounds, pulse remained at 85 and the blood pressure remained at 130/70 mm Hg.

Following operation the basal metabolic rate as shown on the above graph was +18 and remained at this level. The weight had dropped to 139 pounds but then rose steadily. The blood pressure remained at 130/70 mm Hg, and the pulse remained at 90.

Physical Examination The patient was very nervous, restless and fidgety. His skin was wet, his hands were hot and moist. There was an obvious fine tremor of his extended fingers and hands. There was a definite prominence of his right eye with upper lid lag and weakness of convergence. The left eye showed some staring. The tongue exhibited a fine tremor. No lymphatic adenopathy was present.

ent in the neck. The thyroid was diffusely enlarged being three times the normal size with the right lobe slightly larger than the left. It was soft in consistency. No bruits or thrills were noted and no nodules were present. The trachea, thorax and lungs were normal. The heart was not enlarged and gave a normal percussion outline, a forceful apical impulse, sounds loud and ringing with a $P > A_2$ and a soft blowing systolic murmur localized to the mitral area. The blood pressure was 172/62 mm of mercury. The radial pulse was rapid, regular and bounding. The abdomen, back, loins and extremities gave normal findings. The neurological examination also was normal.

Laboratory Data. The white cell count throughout the course in the hospital was within normal limits. The leukocytes varied between 6650 with 59 per cent neutrophils, 40 per cent lymphocytes and 1 per cent basophils on May 3, 1945 to 5450 with 52 per cent neutrophils, 44 per cent lymphocytes and 4 per cent eosinophils on August 16, 1945. **Urinalyses.** All specimens were normal. **Blood Kahn** on May 1, 1945 was negative. **Blood Cholesterol** values varied between 175 mg per 100 cc. on May 3, 1945 and 213 mg per 100 cc. on June 26, 1945. **Basal Metabolic Rate Determinations** are shown graphically in Figure 54. **A ray Examination of Chest** Negative. **Electrocardiogram** Normal on May 3, 1945, June 21, 1945 and July 2, 1945. **Consultations.** Eye, Exophthalmic measurements were within normal range. **Ear, Nose and Throat.** Normal vocal cords normal in appearance and motion on phonation and respiration.

Course. Thiouracil therapy (Deracil) 0.2 gm three times daily was begun on May 8, 1945. No liver extract was administered. From then on the patient's progress was very satisfactory. He gained weight, became gradually less and less nervous and restless. His pulse declined to a normal rate and his blood pressure became normal. All these changes ran parallel with the decline of his basal metabolic rate to a normal level. On June 2, 1945 thiouracil was discontinued and **Legol's solution**—10 drops three times a day after meals—was begun, and on June 11, 1945 he was operated upon; a subtotal thyroidectomy was done. The postoperative course was uneventful and the wound healed well. The patient was transferred back to the Medical Service on June 20, 1945. He was given a thirty day furlough on July 9, 1945. At the end of his furlough the basal metabolic rate was +6 per cent, the pulse 82, weight 150 pounds and blood pressure 174/72 mm of mercury.

Group II

CASE II.—Private, 19 years of age, white. Length of service, one year and one month. Admitted April 13, 1945.

Family History. This was not contributory. There was one sister who had bronchial asthma of a moderately severe degree. **Previous Personal History.** Negative. **History of Present Illness.** This soldier's symptoms began on February 19, 1945. He first noticed that he was becoming more and more nervous. This increased rapidly in degree and he became very restless and fidgety. He noticed concomitantly with this nervousness an increase in appetite, but there was no increase in his weight. He had lost 21 pounds in weight in his first four months in the Army but thereafter his weight remained constant. Definite intolerance to warmth developed. He preferred windows opened even in winter and slept without covers. Profuse perspiration had become a troublesome symptom. Palpitation with tachycardia had been noticed frequently on even slight exertion and there had been with this some slight degree of shortness of breath. No gastrointestinal symptoms developed. Enlargement of the neck had been noted but only after his attention was called to it.

Physical Examination. The patient was a nervous, restless, fidgety soldier of good nutritional status and good hemie component, somewhat asthenic in type. The skin was smooth and moist, the hands hot and wet. There was a fine con-

stant tremor of the extended hands and fingers. The eyes revealed no exophthalmos and there was no lidlag or conversion before operation. The thyroid gland was enlarged to about three times the normal size, the right lobe being slightly

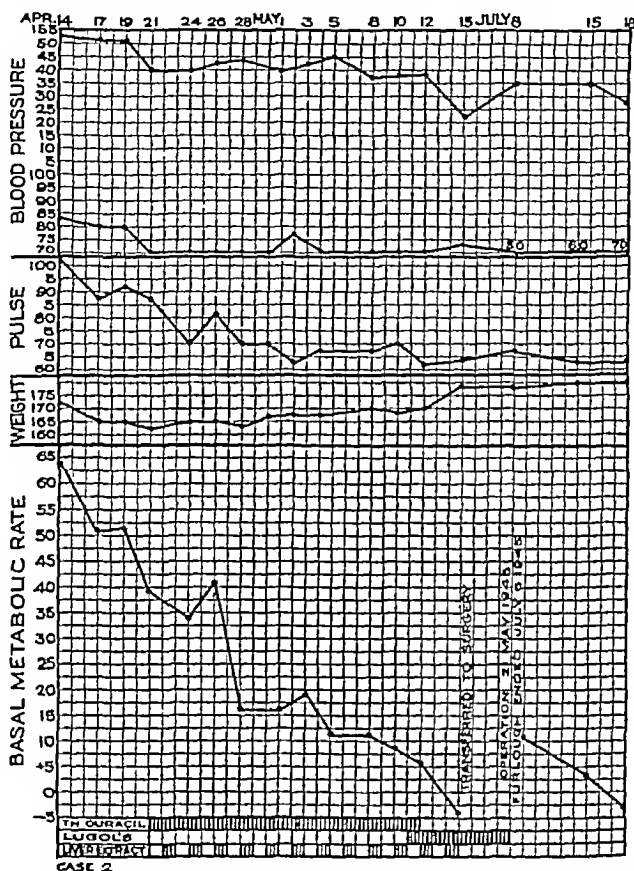


Fig 55—Course of the blood pressure, pulse, weight and basal metabolic rate in Case II. Upon admission the basal metabolic rate was +64, weight 172 pounds, blood pressure 152/82 mm Hg. With rest in bed the basal metabolic rate dropped to +38, there was a loss in weight of 7 pounds. Pulse dropped to 90 and blood pressure to 140/70 mm Hg, when thiouracil therapy was started on April 21, 1945. Thiouracil was discontinued on May 12, 1945 at which time the basal metabolic rate was +6, weight 170 pounds, pulse rate 62, blood pressure 137/70 mm Hg. Lugol's solution was administered on May 10 and discontinued on May 18 when the basal metabolic rate was -5, weight 179 pounds, pulse rate 67 and blood pressure 134/60 mm Hg. Operation took place on May 21, 1945. Following operation the basal metabolic rate was +10, weight 179 pounds, pulse rate 64, blood pressure 135/70 mm Hg. After a thirty day furlough the basal metabolic rate was -3, weight 180 pounds, pulse rate 64, blood pressure 124/60 mm Hg.

larger than the left and the isthmus also being enlarged. A blowing systolic murmur was heard over both lobes. The gland was soft in consistency and smooth. A pulsation of the entire precordia was noted but the apex impulse was felt at the midclavicular line in the fifth left intercostal space. The percussion outline

was normal. The pulse was 120 beats per minute and the blood pressure 152/82. In the extremities only bilateral quadriceps weakness was significant. Neurological examination was essentially negative. All the tendon reflexes were hyperactive. *X rays* Chest plate normal. *Electrocardiograms* Normal on four occasions. *Exophthalmometer* showed a change of 3 mm in each eye during thiouracil therapy. *Ear, Nose and Throat* Normal before and after operation.

This soldier's course in the hospital was quite uneventful. Beginning on April 23, 1945 he was treated with thiouracil in doses of 0.2 gm. three times daily. Liver extract, 1 U.S.P. unit was administered intramuscularly every other day. As treatment continued the patient became less restless, less fidgety, perspiration decreased and tremor became less marked. The pulse gradually slowed to a rate of 66 to 70 beats per minute. The average blood pressure reading was 130/76 just before operation. He showed a steady gain in weight. On May 12 thiouracil treatment was stopped and Lugol's solution—10 drops three times per day after meals—was given. Subtotal thyroidectomy was performed on May 20. The post-operative course was uneventful and the wound healed well. The basal metabolic rate, pulse, blood pressure, eye and ear, nose and throat were normal. The blood counts, urinalyses and blood serology were normal. The blood cholesterol values varied between 198 mg per 100 cc. on April 14, 1945 to 220 mg per 100 cc. on July 12, 1945. *Basal Metabolic Determinations* are shown in Figure 55.

Case III—A soldier aged 45 years.

Family History Father died of high blood pressure, otherwise the history is noncontributory. *Previous Personal History* Hemorrhoidectomy at sixteen years of age. *Present Illness* The patient states that he had been very nervous all his life. As a civilian, five years ago he was treated for this condition. He has been a heavy drinker consuming 2 to 6 quarts of whiskey per week until he came into the Army since which time he has averaged only one or two drinks per day. However his present condition apparently had its onset in the summer of 1944. At that time his nervousness began to increase. Subsequently he had suffered a loss of 35 pounds in weight, associated with a decrease in appetite. Frequent trembling spells had developed, perspiration had become profuse and palpitation with precordial aching and dyspnea had become a frequent and disturbing symptom. He developed a definite intolerance to warmth. The enlargement in his neck became noticeable about five months before admission and has increased to date. His right eye has been noted to have become more prominent than his left.

Physical Examination. This patient appeared much older than his stated age. He was thin and underweight but exhibited a good hemic component. The skin was warm and moist. A fine rapid tremor of the extended fingers and hands was present. Bilateral quadriceps weakness was present. The right eye was more prominent than the left and upper lid lag was present. The tongue exhibited a fine tremor. The thyroid gland was enlarged, right lobe being larger than the left, firm and smooth and no murmurs were detectable. The lungs were normal, the heart of normal size and position and with a normal percussion outline and sounds of good quality. A fairly loud blowing systolic murmur was heard over the mitral area, transmitted to the axilla. The pulse rate was 120 beats per minute, the blood pressure 144/66 mm of mercury.

Laboratory Data The white blood cells varied between 6800 (neutrophils 65 per cent, lymphocytes 35 per cent) on July 3, 1945 to 7800 (neutrophils 52 per cent, lymphocytes 46 per cent and eosinophils 2 per cent) on August 16, 1945. The *Blood Kahn Reaction* and *Urinalyses* were negative. The *Blood Cholesterol* values varied between 183 mg per 100 cc. on July 3, 1945 to 193 mg per 100 cc. on July 28, 1945. *Basal Metabolic* rates are illustrated in Figure 56. *X ray* examination of the chest was negative. *Electrocardiograms* Normal. *Eye Confrontations* Exophthalmometer measurements were within normal range and showed no significant change during the patient's stay in the hospital.

Course Thiouracil (Deracil) therapy was begun on July 6, 1945, a dose of 0.2 gm being given three times daily with liver extract intramuscularly. The patient became less restless, gained in weight, and his blood pressure and pulse gradually returned to normal levels coincident with the decline of the basal metabolic rate to a normal level (Fig 56). Thiouracil therapy was discontinued

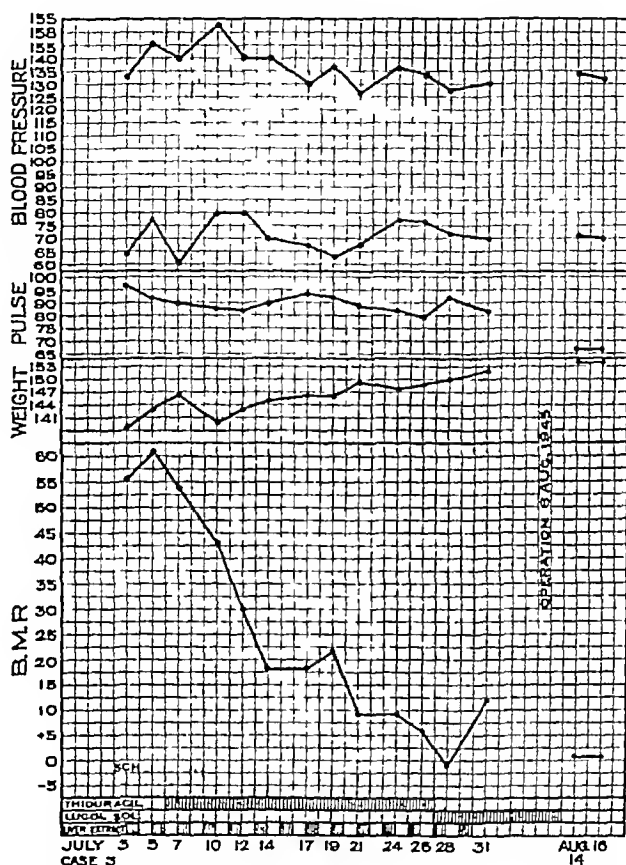


Fig 56—Course of the blood pressure, pulse, weight and basal metabolic rate in Case III. Thiouracil therapy was started on July 6, 1945 at which time the basal metabolic rate was +62, weight 143 pounds, pulse rate 92 and blood pressure 155/72 mm Hg. A marked drop in the basal metabolic rate and a gain in weight took place with the thiouracil therapy. The thiouracil was discontinued on July 26, when the basal metabolic rate was +3, weight 150 pounds, pulse rate 90 and blood pressure 130/70 mm Hg. Lugol's solution was administered between July 26 and August 6, 1945. Thyroidectomy was performed August 6. Following the operation the basal metabolic rate was +2, weight 155 pounds, pulse rate 68 and blood pressure 132/70 mm Hg.

on July 26, 1945 and he was given Lugol's solution, 10 drops three times a day, after meals. Thyroidectomy was performed on August 6, 1945. The postoperative course was uneventful. Basal Metabolic Rate August 14 and 16, +1. Weight August 14 and 16, 161 pounds. Pulse August 14 and 16, 68. Blood Pressure August 14, 133/72, August 16, 132/70.

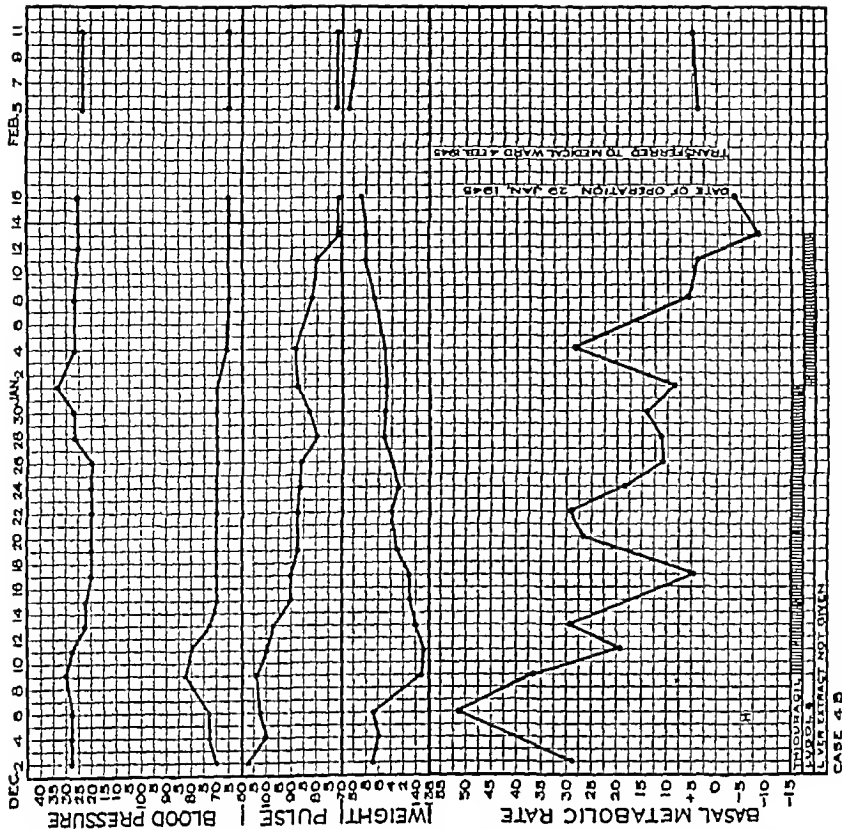
RESULTS OF TREATMENT WITH THIOURACIL

Preoperative—As noted in Table 1, all patients, except L.Z., showed a definite drop in the metabolic rate after treatment with thiouracil. Column 1 indicates the number of days of thiouracil treatment necessary to prepare the patient for the optimum preoperative state. Column 2 indicates the drop in metabolic rate (per cent), i.e., the difference in percentage of metabolic rate between rate when thiouracil started and rate when patient was considered prepared sufficiently for Lugol's solution. The case of L.Z. was incomplete. This patient gave a history of somnambulism over a long period. While under treatment the patient had several episodes of somnambulism and it was decided to transfer him to another general hospital. We did not attribute any of his symptoms to thiouracil.

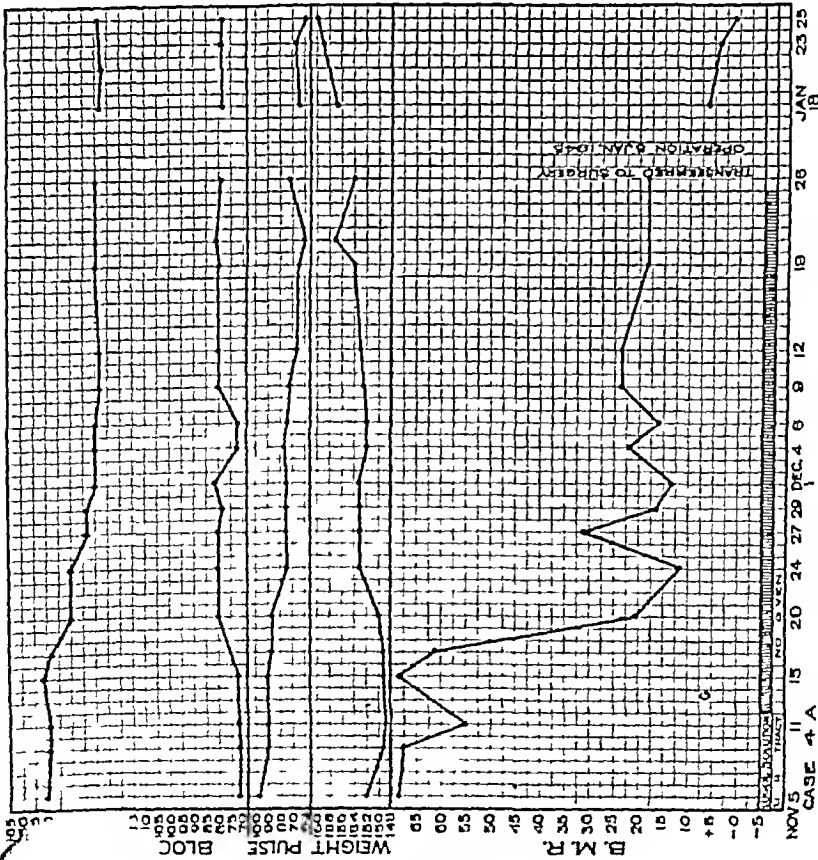
All patients responded to thiouracil. The response in lowering the basal metabolic rate was more rapid and pronounced in some cases than in others. Bartels¹⁰ found that approximately one day of treatment with 0.6 gm. of thiouracil was required for each per cent of elevation in the basal metabolic rate, but if the patient received the Lugol's solution before the administration of thiouracil the response was slower. With this knowledge the date of readiness for operation could be predicted. This was not true in our series. The response was rapid in some cases, especially those which at the onset showed a high basal metabolic rate. In other cases the response was slow. No patients in our series had received Lugol's solution prior to the administration of thiouracil, therefore that factor did not enter into a slow response.

As stated in our plan of treatment, when a patient fulfilled the criteria set for optimum preoperative state, Lugol's solution was given for approximately ten days. During this period all cases showed a progressive but variable fall in the basal metabolic rate, more marked the first three days after the administration of the Lugol's solution. One can assume that this response is partly a thiouracil effect. In some cases the reduction was dramatic as shown in Figures 55, 56 and 58 (case of B.A.). In others it was slow as illustrated in Figure 58 (case of K.M.). There was no difference in the response between cases of Group I and Group II. The administration of liver extract did not influence the effect of thiouracil upon the basal metabolic rate.

It is well to note that the normal basal metabolic rate may be as low as minus 18. When a patient develops thyrotoxicosis the rate may not exceed plus 10 or plus 15 which, in turn, may be normal values for other subjects. This was true in the case of one of the members of the Women's Army Corps, who with a severe thyrotoxicosis never recorded a basal metabolic rate above plus 22. It was noted that in this case the basal metabolic rate fell slowly. The pulse showed a slow fall to normal and there was a moderate increase in weight. The tremor of the hands and tongue and 'sweaty palms' disappeared just



Preparation with Lugol's Solution Only



Preparation with Thioracil and Lugol's Solution

Fig. 57—Comparison of the records of the blood pressure, pulse, weight and basal metabolic rate of a patient prepared for operation with Lugol's solution but with no thioracil and no liver extract, and a patient prepared for operation with thioracil and Lugol's solution, but with no liver extract. It will be noted that in the first case the patient at first showed a sudden drop under therapy with Lugol's solution, but later maintained a constant level. There was some gain in weight, slowing of the pulse rate, and a decrease in the pulse pressure. The Lugol's solution adequately prepared this patient for operation. The second chart illustrates the more rapid drop in the basal metabolic rate under thioracil therapy in a shorter period of time. This drop was from +52 to +40 in 16 days after which the rate was maintained at this level. There was no gain in weight during therapy. The pulse rate lessened but no remarkable change was noted in pulse pressure. A comparison with Figures 54, 55 and 56

TABLE 1—RESULTS WITH THIOURACIL THERAPY

Case	No of Days Thiouracil Therapy Required	Percentage Drop in B.M.R. During This Period	Pulse Drop	Change in Weight in Pounds
A P	27	+27 to +4 23	106-86	+8
D T	14	+32 to +9 23	104-84	-3½
K.M.*	21	+38 to +9 29	102-80	+2
T.L.*	23	+24 to +11 13	98-72	+12
B W* †	47	+49 to +9 40	108-80	+15½
S.S.*	19	+53 to +6 47	110-78	+2½
B.A.	25	+52 to +12 40	128-76	+20
H J	23	+52 to +7 45	108-88	-2
M.R.*	37	+43 to +12 31	103-70	+8
S.A.*	21	+64 to +6 58	104-62	-2
P.M	22	+29 to +9 20	88-62	5
P W	30	+54 to +11 43	92-78	12
M J*	11	+34 to +14 20	92-84	-2
M W*	14	+32 to +6 26	130-94	+3
S.B.*	9	+29 to +4 25	104-78	+12
G.L.	13	+20 to +9 20	98-80	+2
S.E.	29	+30 to +11 19	132-82	+2
L.Z.*	Incomplete	Patient transferred to another general hospital because of somnambulism		

* Liver extract given.

† Developed agranulocytosis.

prior to the approach of the basal metabolic rate to minus 8 which in this case was considered normal

Weight All but four patients gained weight (see Table 1) The maximum weight loss over the entire period of treatment among the four patients who lost weight was $3\frac{1}{2}$ pounds The gain, in general, was steady following the first few days of treatment Patients continued to gain in weight after thiouracil was discontinued and the Lugol's solution was administered, the increase during this period was not more rapid than during the period when the thiouracil was administered **Pulse** All patients showed a steady fall in pulse rate The average drop in pulse rate was 29 (see Table 1) **Blood Cholesterol** In all cases there was a consistent rise in the blood cholesterol concentration as the metabolic rate fell

The changes in *blood pressure* were variable. The majority showed a consistent drop in pulse pressure concomitant with the fall in the metabolic rate.

The changes in the *thyroid gland* were variable. In some subjects the gland became smaller and firmer. In a few it became larger and firmer.

Toxic Reactions—The literature contains many reports of toxic reactions following thiouracil treatment. These reactions have been varying in degree and severity. Reveno¹⁸ reported gastric distress in the form of pain, burning and gnawing at the onset of five of his cases. This was promptly relieved by the taking of food with the medication. One patient was reported suffering from chills and fever ten days after starting treatment. This lasted two days but ceased after the drug was stopped. None of the above symptoms was noted in our series.

Palmer¹⁹ reported that microscopic hematuria and crystalluria occurred in three cases before sodium bicarbonate was added to the routine therapy. We encountered no cases of microscopic hematuria or crystalluria.

Clute and Williams¹² report that certain patients, perhaps 10 per cent, have complications, from thiouracil therapy, of sufficient degree to necessitate discontinuance of the drug. In our series of twenty-three cases, only one patient developed a complication serious enough to necessitate withdrawal of thiouracil. Clute and Williams¹² observed a morbilliform rash, with itching which disappeared although treatment was continued. Three patients developed urticaria, two of whom developed joint pains and fever necessitating cessation of the drug. These writers advised that thiouracil should be given with great care to any patient known to have allergic symptoms. Bartels¹⁶ reported skin eruptions in three patients. The skin eruptions were generalized purely macular papular in type and pruritic. Relief was prompt on stopping treatment. No rashes or skin symptoms were encountered in our series. Bartels¹⁶ also reported edema of the arms and

legs at the end of the treatment in two patients. The appearance of the skin resembled the early stage of scleroderma. These patients were not myxedematous. We did not observe this complication.

Moore and his associates¹⁵ reported four cases of oral infections possibly related to the drug, and a generalized adenopathy. All symptoms subsided upon cessation of the drug. These investigators also report two cases of fever associated with drug sensitivity and Bartels¹⁶ reported for such cases. Neither oral infections nor febrile responses to the therapy were observed in our study.

Miscellaneous toxic reactions reported by others, some of which were possibly due to thiouracil, were headache, jaundice, enlarged lymph glands, diarrhea and enlarged salivary glands. In one case there was hemorrhage into the thyroid gland supposedly caused by increased vascularity due to thiouracil. We did not encounter any of the above.

The most serious toxic effect noted resulting from thiouracil is neutrophilic leukopenia or *agranulocytosis*. All investigators have reported encountering this complication in varying degrees of severity at one time or another in their series. Astwood,⁹ Williams and Clute¹¹ reported this complication in their early cases. It was believed that in one of these cases much larger doses of thiouracil were used than are now believed necessary. Moore and his associates¹⁵ reported two cases in which the white cell count fell to the neighborhood of 2500 but the polymorphonuclear leukocytes never fell below 30 per cent. In one case the drug was continued with a return of the count to normal. In the other the drug was stopped. Bartels¹⁶ reported the development of leukopenia in three cases in his series of the first 100 patients who were treated preoperatively with thiouracil. This occurred after two, eight and ten months of treatment, the dose of thiouracil being 0.3, 0.1 and 0.05 gm daily respectively. The changes were quite sudden with a reduction in the total white count and the polymorphonuclear cells. He further reported a quick return of the blood to normal following discontinuance of the drug. One case in his series presented the early stages of agranulocytic angina.

Kahn²³ reported a fatal agranulocytosis resulting from thiouracil—it is believed that severe diabetes mellitus was a contributory factor. Nine of the first twenty-two patients treated by Palmer¹⁹ developed transient leukopenia. As soon as the white blood cell count reached 4000 the drug was discontinued for a minimum of seventy-two hours. The depressant effect was always transient and lasted usually about forty-eight hours. No depressant effect was noted after treatment with thiouracil had been resumed.

Thiouracil has been given in more than 2000 cases and there have been seven known fatalities from agranulocytosis. In our series, one patient developed agranulocytosis. This was in Group II, the group

in which liver extract was given. This case will be published fully at a later date

This patient was a 29 year old soldier who served over four years on active duty. His first complaint was in September, 1944 eight months prior to admission to the hospital. In this case, administration of thiouracil was started in a dosage of 0.2 gm. three times a day with 1 U.S.P. unit of crude liver extract given intramuscularly on alternate days. The diet and vitamins were prescribed as indicated under the plan of treatment. The patient slowly improved. His weight increased from 138 to 158 pounds. His symptoms subsided, the basal metabolic rate dropped to 9 per cent on June 19. On June 20 thiouracil was discontinued. Counts taken on June 19 were: white blood cells 5100, neutrophils 61 per cent, lymphocytes 38 per cent, eosinophils 4 per cent. On June 21 the count was: white blood cells 3200, neutrophils 54 per cent, lymphocytes 38 per cent, eosinophils 5 per cent, monocytes 3 per cent. Suddenly on June 23 neutropenia appeared. At that time the patient felt very well. The count on that date was: white blood cells 4800, neutrophils 5 per cent, lymphocytes 80 per cent, eosinophils 15 per cent. Liver extract was then given daily. Pentnucleotide and yellow bone marrow treatment was begun and 500 cc of whole blood was given. On June 24 the patient developed a sore throat and an elevation of temperature to 101° F. On June 25 the count was: white blood cells 3000, neutrophils 6 per cent, lymphocytes 76 per cent, eosinophils 18 per cent. On June 27 the count was: white blood cells 1600, neutrophils zero, lymphocytes 86 per cent, eosinophils 11 per cent, monocytes 3 per cent. The temperature rose to 103° F. On June 29 the patient began to feel better. On that day the blood count showed the first real change with the appearance of 5 stab cells, although an indication of improvement had been given by the appearance of an occasional myelocyte or metamyelocyte in the previous twenty four hours.

Penicillin was begun on June 23. Lugol's solution was given in doses of 10 drops three times a day after meals throughout the neutropenic period. The patient made a slow recovery with gradual improvement in his white blood count. On July 3 the white blood cell count was 6000, neutrophils 61 per cent, lymphocytes 34 per cent, eosinophils 3 per cent, monocytes 2 per cent. Thyroidectomy was performed on August 13, 1945. The patient had a smooth post-operative course.

Table 2 shows a comparison of blood studies in four cases—two from Group I, treated with thiouracil and Lugol's solution and two from Group II, treated with thiouracil, Lugol's solution and liver extract (1 U.S.P. unit) on alternate days.

A review of this table reveals no marked difference in the blood pictures of all four cases. It will be noted that thiouracil at no time had a depressant effect, in fact, the neutrophils increased remarkably during thiouracil administration.

An analysis of all the cases of Group I and Group II shows that the administration of liver extract had no appreciable effect upon the blood picture. In fact, our only case of agranulocytosis occurred in the group receiving liver extract on alternate days during the administration of thiouracil. It is well to note that in this case of agranulocytosis, thiouracil was discontinued three days before the sudden onset of neutropenia. One cannot but be impressed that in the treatment

of patients with thiouracil, the total white cell and differential counts should be observed closely and frequently. We feel that when the white cell count falls to 4000 or neutrophils show a drop to 40 per cent, daily blood counts should be made. Thiouracil should be discontinued when the white blood cell count falls as low as 3500 or the differential count shows a fall to 30 per cent neutrophils.

As stated previously, a close liaison was kept between the surgical and medical service. Frequent consultations were held. The ophthalmologist was consulted before treatment, during treatment, and just prior to operations. Measurements by exophthalmometer were taken on all patients. The changes in readings were not significant. All were within 1 to 4 mm of exophthalmos, and were of the "thyrotoxic" variety.

TABLE 2—BLOOD CHANGES UNDER TREATMENT WITH THIOURACIL

No Liver Extract Given							
Case A P	Hgb %	W B C. Count	Differential Count				
			Neutrophils	Lymphocytes	Eosinophils	Monocytes	Basophils
3 May	12.5	5400	64	34	2		
Thiouracil started	0.2	Gm T I D					
5 May	15.0	6650	59	40			1
8 May	13.5	5900	68	32			
12 May	15.0	5100	54	46			
16 May	14.5	7200	61	37	1	1	
19 May	14.0	6200	66	33	1		
22 May	15.0	6000	38	62			
26 May	14.5	6300	64	36			
28 May	14.0	6300	68	32			
29 May	15.0	7000	68	32			
31 May	16.5	5800	70	30			
2 June	15.0	8700	61	37		2	
Thiouracil discontinued,		Lugol's given					
5 June	15.0	8400	52	48			
26 June	15.5	5300	54	46			
16 Aug	15.5	5450	52	44	4		
Case P W							
30 Jan	14.5	4800	40	54		6	
7 Feb	13.4	7100	37	58		5	
17 Feb	17.0	6000	42	57	1		
19 Feb	16.0	6700	58	40	1	1	
Thiouracil therapy begun							
24 Feb	17.5	5000	49	51			
26 Feb	16.5	6800	50	48	2		
28 Feb	17.0	5650	55	40	2	3	
3 Mar	13.4	7540	68	32			
8 Mar	16.5	7800	73	25	2		
10 Mar	13.8	6350	63	36		1	
15 Mar	17.2	6690	61	31	3		
17 Mar	16.8	8650	65	31	1	1	
21 Mar	16.5	8350	60	37	2	1	
Thiouracil discontinued							
27 Mar	15.3	9800	68	32			
29 Mar	15.3	8300	59	41			
31 Mar	16.9	8750	60	39	1		
5 Apr	15.3	7500	65	31		1	
20 Apr	16.8	6450	62	38			
4 May	17.2	8650	52	48			
8 May	16.3	8700	52	48			
15 May	16.8	6800	51	49			
16 May	15.3	6700	56	42		2	

Liver Extract Given

Case S.S.							
2 July	16 0	8100	36	64			
3 July	16 0	6800	63	35			
Thiouracil therapy begun							
5 July	15 0	8800	56	55			
7 July	15 5	6500	57	40	3		
10 July	16 0	7900	55	44	1		
12 July	16 0	5400	58	40	2		
14 July	15 5	6950	49	51			
17 July	16 0	5700	52	48			
19 July	15 0	6600	57	39	4		
21 July	14 0	7400	40	54	6		
24 July	15 5	5100	64	36			
Thiouracil discontinued							
26 July	15 0	6100	53	46	1		
28 July	16 0	5700	54	46			
31 July	15 5	6900	66	34			
3 Aug.	16 0	6700	62	36	2		
16 Aug.	16 0	7500	52	46	2		
Case S.A.							
13 Apr.		6200	70	26	4		
Thiouracil begun							
19 Apr.	15 0	3550	73	27			
21 Apr.	14 0	6000	60	37	3		
24 Apr.	13 0	5400	54	44	2		
26 Apr.	15 0	5700	58	42			
28 Apr.	17 5	8250	54	26			
1 May	15 5	7100	44	50	6		
3 May	13 0	5300	42	48			
Thiouracil discontinued							
5 May	15 5	6100	63	34	3		
12 May	15 0	7000	68	32			
15 May	14 5	9600	68	41			1
19 May	14 5	6800	61	37	1		
22 July	16 5	8200	62	34	1		3

CONCLUSIONS

1 Thiouracil is a valuable agent in the preoperative management of the thyrotoxic patient, especially when followed by Lugol's solution for a period of ten days after maximum benefit has been obtained from thiouracil

2 No serious toxic effects save one case of agranulocytosis were noted

3 The white blood cell counts must be followed closely and checked frequently while these patients are under treatment with thiouracil. The counts should be followed at least three days after thiouracil is discontinued

4 Crude liver extract, 1 USP unit intramuscularly on alternate days, did not prevent the development of agranulocytosis in one patient receiving thiouracil

5 The operative and postoperative course of patients prepared for operation with thiouracil and Lugol's solution has been satisfactorily uneventful. No surgical complication was encountered which could be attributed to thiouracil therapy

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correlation with the gastroscopic appearance of the stomach. Attention repeatedly has been directed to the fallacy of correlating the character of the gastric submucosa to the mucosal appearance of the stomach. The functional character of the stomach in respect to secretion often is independent of the mucosal appearance. There are not inconsiderable differences of opinion among competent observers concerning the character of the gastric mucosa at the time of a given gastroscopic examination. Striking variations in the character of the gastric mucosa are recorded in the same patient on subsequent examinations. The changing character of the mucosa when varying amounts of air are pumped into the stomach has been the source of comment. Between the personal equations of different observers and the changing character of the gastric mucosa, it is not surprising that a variety of opinion exists concerning the validity of any single gastroscopy.

Value of Gastroscopy in Certain Gastric Lesions—Let us consider the information one expects to obtain from gastroscopy in specific gastric lesions.

1 *Gastritis*—Schindler divides gastritis into (a) superficial, (b) atrophic, (c) hypertrophic and (d) postoperative stomach. These divisions are not mutually exclusive. One may find degrees of each in the same stomach. Superficial gastritis of severe degree is rare in my experience. Minor degrees of gastric irritation are common, and frequently the cause and significance are matters purely of speculation. The late picture of atrophic gastritis is striking and in mild or moderate degree the recognition is not easy. Severe hypertrophic gastritis especially with thick nodular folds is easily identified. The pig-skin character of early hypertrophic gastritis may be difficult of recognition and its significance again is a matter of speculation. An analogy between this appearance and the surface appearance of the tongue and the rectal mucosa is interesting. Atrophy of the papillae of the tongue frequently causes comment but I am not aware of any profound clinical deductions to be drawn from an apparent thinning or atrophy of the rectal mucosa. "Schindler's postoperative stomach" seems to represent merely irritation near the site of a stoma at which there is an artificial juxtaposition of stomach and small bowel mucosa. Reference previously has been made to the difficulty of correlating the clinical findings and gastroscopic appearance of gastric mucosa. The degree and character of peristalsis, especially in the gastric antrum, may furnish some information regarding submucosal infiltration or inflammatory changes.

2 *Gastric Ulcer*—We gastroscope all patients with gastric ulcer in which there is no contraindication to the procedure. A gastric ulcer may be visualized long after its disappearance has been reported by roentgen examination. Occasionally, small gastric ulcers are seen which were not reported by x-ray, however, expert roentgenography rarely fails to locate a gastric ulcer except where the lesion is very

small. It is interesting to observe the healing of a benign gastric ulcer by repeated gastroscopy but the value to the patient is negligible except in instances where malignancy is expected. Gastroscopy may be of significant value in determining whether or not a gastric ulcer is malignant, however, in cases with indeterminate appearances we prefer resection of the ulcer to fruitless gastroscopic speculation. When the pathologist cannot be certain of the benignancy of the resected specimen prior to microscopic examination, it seems useless to expect gastroscopy to make the differentiation *in vivo*.

3 *Gastric Malignancy*—In only rare instances will gastroscopy furnish much additional information in well defined cases. Most surgeons prefer to determine resectability at the operating table by direct inspection rather than accepting a prior gastroscopic opinion, a preference with which I am in accord. Late gastric involvement such as may be demonstrated by x-ray rarely requires gastroscopic confirmation. In early prepyloric lesions gastroscopy may aid in detecting malignant mucosal changes but a negative gastroscopic report must be interpreted with reservation, since it is possible to confuse the pylorus with the distal normal antral mucosa immediately proximal to a prepyloric gastric lesion. The difficulty of visualizing adequately the antrum in the fish hook type of stomach is well known to all gastroscopists and presents a problem quite in contrast with the ease of visualizing the pylorus in the steer-horn type of stomach. The gastroscopic picture of leiomyosarcoma of the stomach especially in instances in which central necrosis has occurred is quite characteristic and is of great aid in differentiating that tumor from other growths.

4 *Benign Tumors*—Gastroscopy may be of great value in visualizing the character of polyps and other benign tumors. Multiple polyps must be differentiated from severe nodular hypertrophic gastritis. The presence of normal gastric mucosa surrounding a benign tumor affords additional data when the question of operation arises.

5 *Indeterminate Roentgen Findings*—In my experience gastroscopy is of the utmost value in cases in which expert roentgenography fails to outline clearly a suspected gastric lesion. I am referring particularly to antral gastric lesions in which the roentgen differentiation between localized hypertrophic gastritis, gastric ulcer, early gastric malignancy and spastic contractions of the muscularis mucosa is most difficult. Truly, the differentiation cannot be made with certainty by gastroscopy, however, visualization of the area in question affords an additional source of information which should not be overlooked.

Safety Factors.—The factor of safety in the average gastroscopic examination must be considered. Relatively few accidents have been reported, however, few observers make a point of reporting their mistakes. I am sure that the true incidence of gastric and esophageal perforations by gastroscopists is far in excess of those reported. There are certain individuals of determination who should avoid performing

any endoscopic examination and it is the duty of those who teach gastroscopy to discourage heavy-handed operators before they become a menace. Unfortunately the inept operator rarely admits his fault.

Contraindications to Gastroscopy—There are certain contraindications to gastroscopy which in degree vary from relative to absolute. They may be listed categorically as follows:

- 1 Any lesion of the esophagus
- 2 Lesions of the cardia in close apposition to the esophageal opening into the stomach
- 3 Mediastinal inflammation or tumefaction
- 4 Moderately severe pulmonary or cardiac disease
- 5 Cirrhosis of the liver or any other condition which gives rise to esophageal varices
- 6 Marked spinal curvature
- 7 Inflammatory conditions of the pharynx
- 8 Marked general debility
- 9 Gross malposition of the stomach
- 10 Recent severe gastric hemorrhage or recent postoperative stomach
- 11 Suspected chronic perforation of a peptic ulcer, gastric or duodenal

To the conservative mind, a safe rule would be to avoid gastroscopy when in doubt about a possible contraindication. Insistence that all candidates for gastroscopy have a thorough roentgen study of the esophagus, stomach and duodenum and that the operator view the films personally will add to the safety of the patient.

Conclusion—Gastroscopy, in the hands of a careful operator, with full cognizance of the dangers, limitations and possibilities of the procedure, is a useful adjunct in the evaluation of certain aspects of gastric disease.

CARCINOMA OF THE COLON AND RECTUM

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CARCINOMA of the large bowel is relatively uncommon in military personnel as compared with other disorders of the gastrointestinal tract. Lesions of this nature, however, are not altogether rare. In the large Army general hospitals in the Zone of the Interior, carcinoma of the colon and rectum is seen sufficiently often to constitute a distinct problem. Twenty-one patients with proved cancer of the large bowel have come under my observation in the course of four years of consecutive service in the gastrointestinal sections of two Army general hospitals in the Second Service Command. In many of these cases little or no suspicion of malignant disease was entertained during the early symptomatic stage. The comparative youth of the patients and the presumed unusual character of their manifestations were misleading features which often lulled the examining officer into a false sense of security. The important lesson drawn from this experience with military personnel is the need for a greater colon cancer awareness among physicians and laity alike. In the hope of contributing toward this end, a review of the subject of carcinoma of the colon and rectum is being presented utilizing our experience with military personnel for purposes of illustration.

INCIDENCE

Of all deaths from cancer about 11 per cent are caused by malignant neoplasms of the colon and 5 to 6 per cent by malignant neoplasms of the rectum and anus. Together these lesions are responsible for approximately 27,000 deaths in the United States yearly. The incidence of malignant tumors of the large bowel in military personnel is not to be estimated from the experience with these lesions in Army general hospitals in the Zone of the Interior. These hospitals would be expected to have the highest incidence in the Army since patients are sent to them from numerous installations which are more directly concerned with servicing troops in the field or in garrisons. Of 1801 soldiers (enlisted men) discharged from the gastrointestinal sections of the Tilton and Rhoads General Hospitals with an established diagnosis between November 1, 1942, and August 31, 1945, seven, or 0.38 per cent, proved to have cancer of the colon or rectum. In addition to these cases, many others were encountered during the same period in officers and in enlisted men who were admitted directly to the Surgical Service.

From the Tilton General Hospital, Fort Dix, New Jersey

ETIOLOGY

Previously existent benign colonic neoplasms, such as adenomatous polyps, may subsequently undergo malignant transformation. Although doubted by some, there is much to support the belief that this sequence of events takes place fairly frequently. The malignancy index in cases of colonic polyposis varies widely. Reports of different observers range from 5 to 85 per cent⁷ with the incidence of malignant change greatest in those polyps found in carcinomatous colons. Very often both the gross and histologic appearance of a colonic neoplasm is such as to suggest that it developed on the basis of a previous polyp (Fig 59). Patients with the heredofamilial type of disseminated polyposis almost invariably tend to develop colonic carcinoma sooner or later. This was the case in one of our patients, a white soldier, aged 26, who had proctosigmoidoscopic as well as roentgenologic evidence of a widely

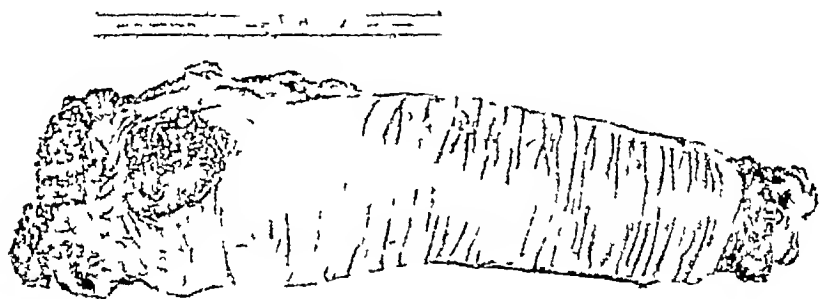


Fig 59—An ulcerated adenocarcinoma of the rectum removed from a 27 year old white soldier. The polypoid character of the base of the lesion, especially at its periphery, suggests that the tumor originally may have been nodular in character and subsequently ulcerated. The appearance also suggests the possibility that the lesion may have had its origin in a preceding polyp.

disseminated polyposis. Carcinomatous changes were shown to be present in several of the polypoid lesions.

The tissues of the intestinal wall of those colons in which a carcinoma has developed have been shown by Dukes¹⁰ and by Bargen, Cromar and Dixon³ to show changes which they construe as potentially malignant. The possibility of a *potentially malignant state in the colon* acting as a precursor to the development of carcinoma is an attractive hypothesis, but it remains to be proved that the changes noted are precursors and not effects of the cancer. *Inflammatory lesions of the colon* may predispose to the development of malignancy. Bargen, Jackman and Kerr⁴ reported an incidence of carcinoma of 3.2 per cent in 871 cases of chronic ulcerative colitis observed by them and Coffey and Bargen¹⁶ reported an incidence of carcinoma in polyposis associated with ulcerative colitis of 25 per cent. Most other investigators,

however, have not encountered such a high percentage of carcinoma in cases of chronic ulcerative colitis. The consensus is that the polypoid lesions of ulcerative colitis may become malignant but probably do so rarely. Diverticulitis has long been thought to predispose to cancer. Most physicians today consider the relationship between diverticulitis and cancer to be incidental rather than actual.¹¹ The important thing to bear in mind is that an individual with diverticulitis may also have a carcinoma. We were misled in this regard in one of our cases, a 52 year old officer with a history of intermittent diarrhea and abdominal pain in whom a barium enema disclosed multiple diverticula with areas of spasm and irritability indicative of diverticulitis. One such area was present at the splenic flexure. A few months after discharge from the hospital the patient was readmitted with an advanced malignancy of the splenic flexure which had eroded through the stomach to form a gastrocolic fistula. Undoubtedly, the malignancy had been present at the time the patient was first seen but was mistakenly attributed to diverticulitis. Still another one of our patients with distinct roentgenologic evidence of diverticulosis of the colon showed areas of irregularity and narrowing in the sigmoid and in the rectosigmoid. These proved to be separate carcinomatous tumors situated in a bowel which was also the seat of a widespread diverticulosis. Anal cancer may take origin in fistulas, fissures, inflamed anal tags and other *inflammatory lesions of the anus*²⁷ but is an exceedingly rare occurrence.

Chronic irritation of the colon, as from constipation and parasitic infestation, appears to play little or no role in the production of cancer. A *predisposition* toward colonic cancer may be inherited⁶ but some exciting factor seems to be required, in addition to the inherited susceptibility, for the actual development of carcinoma.

PATHOLOGY

About two thirds of the malignant tumors of the large bowel involve the left colon and about one-third the right colon.^{13 34} The rectum, sigmoid flexure, cecum and ascending colon, transverse colon, descending colon, hepatic flexure and splenic flexure tend to be involved in order of frequency.^{1 29 35} In this series of twenty-one cases in military personnel, the frequency of involvement was as follows: rectum, 3, rectosigmoid 6, sigmoid flexure, 1, descending colon, 2, splenic flexure, 2, transverse colon, 2, ascending colon, 3 and cecum, 2. In one case two separate lesions were present and in another, not included in the tabulation, several polyps in various locations in the bowel showed carcinomatous transformation.

Adenocarcinomas of the large intestine may be divided for purposes of classification into four main types (1) *Nodular*. This type projects into the lumen as a globular sort of mass which frequently ulcerates. Sometimes, especially in the cecum the tumor adopts an en-

cephaloid or fungoid appearance, grows to a large size, and oozes freely from its ulcerated surface (Fig 60) The connective tissue content is variable but usually is plentiful enough to make the tumor mass hard (2) *Scirrhou*s In this variety the fibrous tissue element is outstandingly prominent, producing an extremely hard, contracted mass As a rule, tumors of this variety are small and give rise to the so-called "napkin-ring" type of growth Intestinal obstruction is frequent The scirrhou

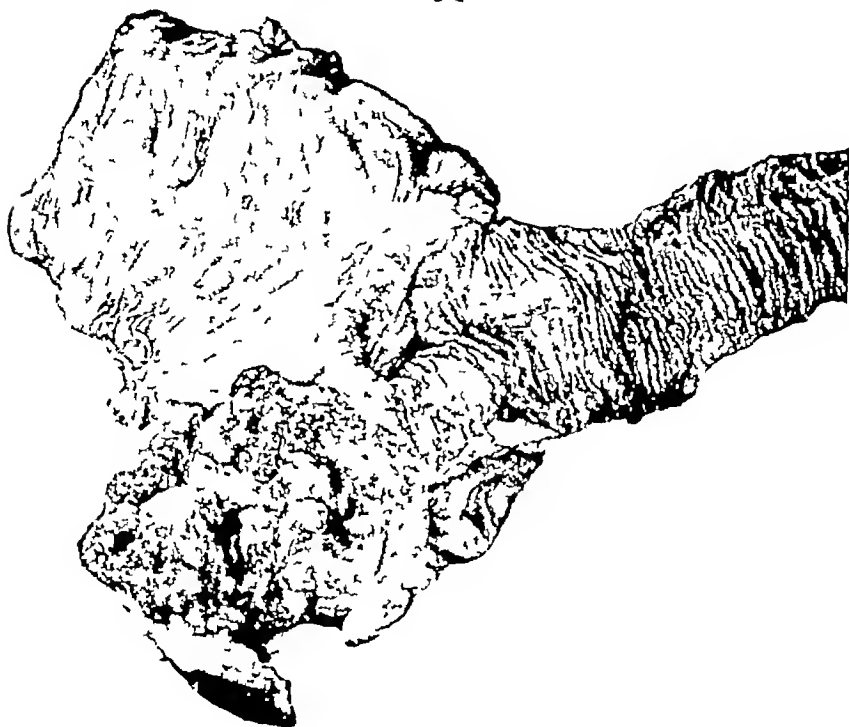


Fig 60—Nodular fungoid adenocarcinoma of the cecum removed from a 39 year old Negro soldier This illustrates the size to which lesions in this region may grow and demonstrates the ulcerative, necrotic character of the base from which sanguineous exudate characteristically oozes

much oftener in the left than in the right colon (Fig 61) (3) *Colloid* This variety of growth is also known as mucoid, mucinous or gelatinous, because of its shiny gelatinous appearance and rich content of mucinous material Tumors of this nature are uncommon They are found most commonly in the rectum and rectosigmoid and in the cecum and ascending colon Ulceration occurs frequently (4) *Papillary* This type resembles a warty excrescence or papilloma Usually shallow ulcerations take place. The tumors are not very common and tend to occur most often in the left colon

Microscopically, adenocarcinomas of the well differentiated variety classically show well-formed glands. These are lined by large columnar cells with a darker than normal cytoplasm and a vesicular hyperchromatic nucleus many of which show mitotic figures. In the poorly differentiated tumors glandlike structures are much less in evidence and the tumor cells tend to appear in masses or cords. In the colloid variety there is an excessive amount of mucinous material both inside the cells and outside in the intracellular spaces.

Adenocarcinomas of the large intestine characteristically grow slowly and are of a relatively low grade of malignancy. Numerous



Fig. 61—Scirrhous adenocarcinoma of the ascending colon. This was found at laparotomy in a 42 year old white soldier who described intermittent right lower quadrant abdominal pain and who showed signs of partial intestinal obstruction and a palpable firm mass in the right lower quadrant of the abdomen. This type of lesion is comparatively uncommon in this portion of the bowel. The great tendency for these lesions to produce narrowing of the bowel and intestinal obstruction is well shown.

schemes have been advanced to classify carcinomas of the large intestine as to their grade of malignancy. The various criteria used include (1) the boundaries reached (Dukes)²⁰, (2) the pace of growth determined by the percentage content of differentiated as compared with undifferentiated cells observed microscopically (Broders)¹⁰, (3) the degree of histologic differentiation⁴⁰, and (4) the amount of mucin demonstrable in the cancer cells, presuming that mucus formation is an expression of intestinal cell function.³¹ About 75 per cent of carcinomas of the colon are Broders' Grade 1 or 2^{20, 32}. Two-thirds of the carcinomas of the right colon and nearly three-fourths of those of the left colon may be classified as Grade 1 or 2³⁶. The majority of rectal

carcinomas are of Grade 2 malignancy and at least 75 per cent are either Grade 1 or 2 Stout⁴⁰ found that only 22 per cent of rectal and 14 per cent of colonic cancers were undifferentiated or poorly differentiated

Widespread *metastasis* may occur with the regional lymph nodes, the liver and the lungs being the most common metastatic sites Metastasis takes place usually in one of three ways (1) by direct extension, (2) through the blood stream, (3) via the lymphatics Of these, the lymphatic route is undoubtedly the most important Careful dissection of all nodes, with or without special clearing of the bowel, has shown that metastasis to the nodes is present in from 65 to 70 per cent of the cases of carcinoma of the rectum^{17, 22, 24} and in about 60 per cent of the cases of carcinoma of the colon¹⁷ The tendency to metastasize is generally greatest in the rectum and sigmoid and least in the cecum This is somewhat remarkable because the lymphatic structures in the cecum and appendix are more extensively developed than in any other segment of the large bowel Regional lymphatic extension is extremely common and widespread in the colloid variety of adenocarcinoma despite the fact that this tumor is slow-growing and late in metastasizing Some interesting features regarding metastasis have been brought to light by the work of Gilchrist and David²⁴ and Collier, Kay and MacIntyre¹⁷ These investigators have shown among other things (1) that age apparently exerts no important influence, (2) that there is no correlation between the size of the lesion and the presence of metastasis, the incidence of metastasis even being higher in persons with smaller lesions than in those with larger ones, (3) that the higher the grade of malignancy the more likely the presence of nodal metastasis, and (4) that retrograde spread and interrupted spread may occur with normal nodes intervening between the primary site and the next nearest involved node

It has been estimated that approximately 5 per cent of colonic neoplasms are multiple and primary^{29 38} This is an important but frequently forgotten feature of adenocarcinoma of the large intestine In the flush of discovery of a neoplasm of the colon or rectum one tends to neglect the remainder of the bowel which deserves also to be surveyed carefully for additional tumors One of our patients showed two separate unrelated primary carcinomas, one in the rectum and the other in the sigmoid flexure Another, previously noted, had multiple carcinomas engrafted on a preexistent diffuse polyposis

CLINICAL ASPECTS

The average age of patients with cancer of the colon or rectum is about 55 years with from 85 to 90 per cent of the cases occurring in persons older than 40 years This very preponderance of the older age group tends to make us forget that approximately 5 per cent of

the cases are persons under the age of 30 years. In the group of twenty-one cases in military personnel the ages ranged from 20 to 59 with an average of 36 years, seven, or 33.3 per cent were less than 30 years of age. The sex ratio in colonic carcinoma is approximately two males for each female. As might be expected, only one of the military personnel group was a female. The ratio of whites to Negroes is difficult to assess because of the variation in the population in the localities from which reports on the subject emanate. In the group of military personnel, two of the twenty-one were Negroes.

A bare majority of patients with malignant disease of the colon and rectum, approximately 60 per cent, seek medical advice within a year after the onset of symptoms, only 20 per cent seek advice within the first three months.²⁰ The average interval from onset to hospitalization is about nine months in cancer of the rectum and one year in cancer of the colon. The duration of symptoms before diagnosis is longer on the average when the carcinoma is in the right colon than when it is in the left colon.

Symptoms—In the early stage of the disease the clinical pattern in colonic carcinoma, regardless of the portion of the large bowel involved, presents no pathognomonic symptoms. Any symptom sufficient to attract attention to the bowel may be a symptom of cancer. Completely asymptomatic cancer of the large intestine in the sense that a lesion may be discovered in a patient without symptoms of altered bowel function, abdominal cramps, pain or abnormal stools is rare. This was true of one of the patients in the group I observed, a 43 year old white soldier who complained of heartburn and rhythmic, postprandial, epigastric pain of an ulcer character. Roentgenologic examination disclosed a deformed duodenal cap consistent with duodenal ulcer. However, on physical examination a huge nodular, hard liver was felt and on barium enema examination an obstructing lesion was demonstrated in the descending colon just distal to the splenic flexure (Fig. 62).

In patients with *carcinoma of the right colon*, constitutional symptoms are prominent and a tumor mass is often palpable while obstruction is not very common. There is some type of abdominal discomfort or distress in at least 75 per cent of the cases. When real pain is present it is usually mild and is commonly indefinitely localized to the right periumbilical area and the right lower quadrant. Almost half the patients describe dyspeptic phenomena such as anorexia, bloating, belching, epigastric fullness, nausea and vomiting. Weakness, fatigue and weight loss are fairly common. Approximately one in four complains of constipation, but this is ordinarily not as marked as in carcinoma of the left colon, it is uncommon in patients with lesions of the cecum. Diarrhea occurs perhaps a little more frequently than constipation. Characteristically no blood is grossly discernible in the stools.

The symptoms that characterize *carcinoma of the left colon* are predominantly those of intestinal obstruction. The obstructive phenomena usually appear fairly early so that evidence of constitutional deterioration develops late in the course of the disease. Ulceration with bleeding is more commonly apparent in the stools. Abdominal pain, which is described in from one-half to two-thirds of all cases, is of variable severity. In the initial stages it may amount to no more than a weighty feeling, an ache, a mild cramp, a dull pain or a feeling



Fig 62—A long malignant stricture of the descending colon just distal to the splenic flexure is clearly shown. This was discovered in a 43 year old white soldier who had no symptoms referable to the large bowel, but who showed striking signs of widespread metastasis with a huge nodular liver.

of gaseousness associated with an increase in expulsion of flatus. The distress usually grows more pronounced as time passes and is succeeded in turn by griping and real colicky pain. Not uncommonly, intestinal obstruction with severe colic and abdominal distention develops rather abruptly and may even be the initial evidence of the disease. Constipation develops for the first time or becomes definitely more pronounced than had hitherto been true, in at least half the cases. The progressive character of the constipation is of the greatest importance. Diarrhea, which is encountered in from 10 to 20 per cent

of all cases, is intermittent. Visible blood loosely attached to the outside of the stool is observed by approximately one-fourth of the patients. Weight loss is to be found in about a third or more of the cases but is a late developing change. Dyspeptic phenomena are uncommon.

Carcinoma of the rectum is characterized in the main by a change in the character of the stool, alteration in bowel regularity and grossly visible bleeding. A gradually progressive alteration in the established bowel habit is one of the outstanding symptoms in patients with a rectal neoplasm. From 85 to 90 per cent of the patients observe blood or bloody mucus on defecation at some time in the course of the disease and the attention of the patient not infrequently is first attracted by this. Pain ordinarily is not severe and is of a minimal character unless the anal sphincters are implicated or the tumor mass comes within the grasp of the sphincteric musculature. Extension of the growth into the perirectal structures or infiltration of the nerves also causes severe and pronounced pain. Characteristically, the pain is more of a distress, described as a weighty feeling in the pelvis or rectum, a sense of fullness about the outlet, soreness, irritation, itching or a mild cramping at the time of stool. Too much emphasis has been placed on the so-called "ribbon" or "pencil" stool as a prominent manifestation of cancer of the rectum. The final form adopted by the stool is determined mainly by the caliber of the anal canal and a tumor mass is of significance in this regard only when it involves the anus itself. Buie¹² found deformed stools in only 14 per cent of 1937 patients of carcinoma of the rectum and sigmoid. Loss of weight and strength is present only in cases with advanced disease and is usually antedated by other symptoms. Dyspepsia is rare unless metastasis has taken place to the liver or upper abdomen.

Physical Findings—The general appearance of a patient with a malignant tumor of the large bowel depends upon the duration of the illness, the stage of the growth and the presence of complications such as abscess formation. In some patients with cancer of the cecum or ascending colon a pallor and sallowness may be seen even though nutrition is still good. If the abdomen is carefully palpated a mass may be found in about a third of all cases, irrespective of the location of the growth in the bowel. It is commonly believed that tumor masses are most often felt when the cancer is in the right colon, but this is open to question. If obstruction is present there may be audible and at times visible hyperperistalsis, abdominal distention and tympanites. Metastasis may be evidenced by distortion, hardening and thickening of the umbilicus, hardening, enlargement and nodularity of the liver, the presence of ascites, enlargement and firmness of the inguinal lymph nodes, the presence of an enlarged palpable left supraclavicular lymph node or enlarged firm nodes in the axillae or at the outer border of the left pectoralis major muscle or by physical abnormalities in the

examination of the lung or demonstrable changes in the lung on roentgenologic examination

Approximately 75 per cent of all rectal tumors are within the reach of the index finger provided a careful and adequate examination of the rectum is performed. Unfortunately, this simple yet important examination is still widely neglected. Not only will digital examination reveal the existence of a lesion, but in the presence of such a lesion it will also give important information as to its size, fixation, attachment to other structures and even the presence of enlarged lymph nodes. It has been estimated that six months is required for a lesion to traverse one-fourth of the circumference of the bowel. By this means a rough idea may be obtained as to the time the growth has been present. Occasionally, vaginal examination will disclose a mass in the rectosigmoid which was not felt on digital exploration of the rectum.

LABORATORY FINDINGS

A variable degree of anemia will be found in about two-thirds of the patients with lesions of the right colon and about one-third of those with lesions in the pelvic colon. Anemia may be the only evidence of a cancer of the cecum or of the ascending colon. At times this may even mimic pernicious anemia. Leukocytosis is not especially common but occasionally remarkable elevations of the white blood cell count are seen, particularly when there is a great deal of necrosis, secondary infection or perforation with abscess formation. Occult blood will almost invariably be found in the stools. There is usually, but by no means always, an increase in the red blood cell sedimentation rate.

PROCTOSIGMOIDOSCOPY

About 75 per cent of cancers of the large bowel develop in portions which may readily be visualized through the proctosigmoidoscope. Not only may the gross characteristics of a neoplastic lesion be observed through the instrument, but also its position, extent of local infiltration, mobility, and distance from the anal margin may be determined. An important adjunct of proctosigmoidoscopy in the presence of a suspicious lesion of the rectum or sigmoid colon is the taking of a biopsy. Too often, however, these specimens are reported by the pathologist as showing no evidence of cancer because no malignant tissue happened to be included in the biopsy. If there is some doubt about the malignancy of the lesion, another biopsy should be taken from near the base of the growth. If, however, the appearance of the lesion very strongly suggests malignancy, especially to a trained sigmoidoscopist, no delay should be countenanced in instituting therapy because of a negative report for carcinoma as determined from a biopsy sample.

Adenocarcinomatous lesions appear through the proctosigmoido-

scope as proliferative masses growing from one wall or encircling the bowel and blocking its lumen. In some cases an ulcerated lesion is seen with a necrotic base and heaped up nodular or polypoid edges. In still other cases the appearance is that of a necrotic tube lined by friable, easily traumatized, possibly polypoid, tissue. Characteristically, there is a fairly sharp line of demarcation between the cancer and the adjacent tissue. Rarely is there sufficient spasm or edema distal to the growth to obscure it. This is a feature of inestimable value in differentiating the lesion from more benign inflammatory states, such as diverticulitis.

ROENTGENOLOGIC FEATURES

Roentgenologic examination in carcinoma of the large bowel is of the greatest usefulness as a means of demonstrating those lesions which are above the reach of the examining finger and beyond the view of the proctosigmoidoscope. If careful observation is made and roentgenograms taken in the oblique and lateral positions as well as the usual anteroposterior one, a diagnostic accuracy of over 90 per cent is to be expected. The use of the double contrast technic, wherein both air and barium are introduced to delineate the contour and mucosal pattern of the bowel, is an additional aid in roentgenologic diagnosis. Occasionally, one encounters a patient who is unable to retain a barium enema in spite of the use of occluding rectal bags and other devices employed by the roentgenologist. In such cases a barium progress meal may reveal the tumor satisfactorily especially if the lesion is in the right colon. If the barium meal is contraindicated in these cases because of intestinal obstruction the introduction of a Miller-Abbott tube to the ileocecal valve and the injection then of a thin mixture of barium through the tube may succeed in delineating the lesion (Fig 63). The lower portion of the bowel is notoriously difficult to examine by x-ray and diagnostic accuracy by this examination does not approach that for other portions of the bowel. Lesions in the flexures of the colon and those on the posterior wall of the cecum are also often difficult to demonstrate and are liable to be missed. Positive findings by x-ray are of the greatest value, but if one relies implicitly on a negative barium enema report one will often be misled. If there is any cause to doubt the findings, the barium enema should be repeated after a course of antispasmodics.

The roentgenologic criteria of malignant infiltration in the large bowel are (1) obstruction to the flow of the opaque medium which is persistent despite manipulation and change in position of the patient, especially if the head of the barium column is blunted and hooked, (2) a persistent filling defect whose outlines are jagged and irregular, particularly if the segment of colon involved is not very long, or (3) a stricture or annular narrowing of the bowel which is persistent and does not respond to antispasmodics.

One should be very wary about forcing enema fluid beyond an area of narrowing and resistance in the large bowel. Small annular lesions of the sigmoid and descending colon may act in a ball-valve fashion, allowing the enema fluid to flow in easily but blocking its outflow. Or there may be some initial resistance to the passage of the opaque fluid followed by a sudden relaxation with a resultant rush of large quantities of fluid under considerable pressure into the bowel above.



Fig. 63—A roentgenogram of the terminal ileum, cecum and ascending colon obtained after introduction of a thin barium mixture through a Miller-Abbott tube in the patient whose specimen is shown in Figure 61. This demonstrates the value of such a procedure in the study of patients with suspected lesions of the right colon which cannot be shown by a barium enema and in whom a barium meal is contraindicated because of the presence of intestinal obstruction.

the lesion. In these cases the distending effect of the trapped enema fluid on bowel probably already weakened and thinned by preexisting obstruction may result in perforation.

COMPLICATIONS

The outstanding complication of adenocarcinomatous lesions of the large bowel is that of *obstruction*. Colic, constipation and abdominal

distention are present in approximately 40 per cent of all patients with cancer of the large bowel. At least three-fourths of the tumors found in the left colon cause either partial or complete obstruction. Obstruction may develop acutely as a result of volvulus, intussusception, sudden clogging of a partially blocked lumen by accumulated fecal matter, or inflammatory changes with edema and swelling. One of the patients I observed, a 38 year old soldier, developed intestinal obstruction abruptly without any premonitory symptoms while in the hospital for the treatment of an unrelated orthopedic condition. At laparotomy a scirrhous adenocarcinoma of the transverse colon was found. Another soldier, 20 years of age, was admitted to a hospital because of the sudden onset of abdominal pain and abdominal distention. Retrograde barium enema study disclosed an obstructing lesion just proximal to the hepatic flexure which had many of the characteristics of intussusception (Fig 64 upper). Following evacuation of the enema the patient was completely relieved of his distress. Another barium enema examination performed at the Tilton General Hospital at a later date showed the intussusception no longer to be present and clearly demonstrated a large tumor mass in the ascending colon (Fig 64, lower).

Acute free perforation of an adenocarcinomatous tumor of the colon sometimes occurs with the development of peritonitis or a localized abscess. We observed this in a 33 year old soldier who suddenly developed severe abdominal pain with fever, leukocytosis and abdominal rigidity. Roentgenologic examination showed a dense fluid collection in the pleural space which was interpreted as an empyema. Injection of air after a diagnostic tap showed the air to be under the diaphragm and established the presence of a subphrenic abscess. This was surgically drained with distinct improvement. Abdominal pain developed during the period of convalescence together with evidence of distention and signs indicating progressing intestinal obstruction. At laparotomy a cecal carcinoma was found which had perforated and given rise to the subphrenic abscess and now had produced obstruction at the ileocecal junction. Invasion of adjoining viscera with the formation of a *fistula* is not too uncommon. Carcinomas of the transverse colon, for example, are especially prone to invade the stomach. Two of the patients in the group I have seen in military personnel had a gastrocolic fistula. In one, an officer 52 years of age, the jejunum was also involved. The remarkable feature of this case was the fact that the initial manifestation was a massive hematemesis without any symptoms referable to the large bowel. *Urinary tract complications* are fairly frequent because of the close anatomical relationship between this tract and the colon and rectum. Fistula formation, invasion of the bladder and obstruction of the ureter with resultant hydronephrosis are among the complications which may occur. At times the urinary symptoms dominate the clinical picture.



Fig 64

DIAGNOSIS

The diagnostic record in carcinoma of the large bowel leaves much to be desired. It is regrettable, but nonetheless true, that an average of nine months to a year elapses before the patient with cancer of the large bowel is admitted to a hospital or a correct diagnosis established. Despite all the advances which have been made in the field of medicine, the diagnosis of carcinoma of the large bowel today is being made no earlier. Much of this is the fault of the laity. The average layman is not conversant with the potential importance of what may appear to be innocent symptoms referable to the colon. For one reason or another, a physician is not consulted until symptoms have been present for some time or until some dramatic symptom such as rectal bleeding occurs which arouses real concern. On the other hand, physicians are not entirely blameless. Many practitioners delay more than seems warranted before arriving at a diagnosis or referring the patient to a responsible clinic. Very often this is due to circumstances beyond the practitioner's control. There seems little excuse, however, for the findings of Braund and Binckley⁹ who reported that of one hundred patients with cancer of the rectum referred to the Memorial Hospital in New York City, 20 per cent had not received a rectal examination. Furthermore, a distressing number of patients are operated on for conditions alien to the major disorder. From 20 to 25 per cent of patients with cancer of the rectum and anus are subjected to hemorrhoidectomy within six months prior to recognition of the malignant lesion.^{28, 29} Approximately 15 per cent of patients with cancer of the right colon undergo appendectomy after the onset of symptoms.³⁰ In addition, about 25 per cent of patients with cancer of the left colon or rectum are given paregoric or bismuth for diarrhea for long periods, or receive vaccines for colitis or sulfonamide compounds for supposed bowel infection.²⁷ It cannot be overemphasized that no patient should be subjected to an anal operation without thorough examination of the colon proximal to the anus. Nor must one treat diarrhea which lasts more than three days without attempting thoroughly to investigate the large bowel by all means available.

Many more patients will be discovered to have carcinoma of the large bowel at a much earlier stage if malignant disease is held suspect

Fig 64.—Upper, Roentgenogram taken during retrograde barium enema study of a 20 year old white soldier complaining of right upper quadrant abdominal pain. Obstruction to the passage of the barium at about the hepatic flexure is seen. There also is well demonstrated the outline of an intussusceptum. Following evacuation of the barium clyster there was an abrupt relief of the abdominal pain.

Lower, Roentgenogram of a barium enema study made on the same patient six weeks later. During the intervening period he had been free of abdominal pain. This roentgenogram shows the intussusception no longer to be present and demonstrates a marked filling defect of the ascending colon just proximal to the hepatic flexure.

in all patients, especially those over thirty years of age, who manifest a change in bowel habit of more than brief duration, or recently acquired abdominal distress related to defecation, or gradual development of increasing abdominal distention and peristaltic unrest. A malignant tumor ought still to be held suspect even if a thorough physical examination discloses some other defect sufficient in itself to produce the symptoms. This is well illustrated by one of our cases, a 44 year old nurse, who was seen because of constipation and abdominal cramping of short duration. Vaginal examination showed the uterus to be markedly enlarged and studded with multiple fibromyomas. A retrograde barium enema study of the colon was made before undertaking hysterectomy in order to make certain that no other cause for the symptoms was present. This disclosed an irregular filling defect in the upper descending colon which proved after resection to be an adenocarcinoma.

TREATMENT

Operative Treatment—The indications for radical surgery in patients with cancer of the colon and rectum have broadened considerably in recent years. This is reflected in the progressive increase in the operability rate so that at the present time about 60 to 70 per cent of all cases of cancer of the colon and rectum are considered worthy of surgical exploration when seen.^{25 26} In approximately 70 per cent of the cases which are explored resection is done. This represents an average resectability rate at the present time of about 50 per cent.^{1 15 32} Extension to adjacent organs is today no deterrent to radical surgery, all or part of some of the neighboring viscera or somatic structures may be sacrificed in order to accomplish the removal of a colonic cancer. Cattell and Sugarbaker¹⁴ estimate that from 15 to 20 per cent of successfully resected lesions require the removal in part or whole of some adjacent structure. Involvement of the lymph nodes and even distant metastasis to the liver are not necessarily contraindications to radical resection of the primary tumor. If the metastatic lesions in the liver are not numerous, death may be delayed some and the patient rendered much more comfortable during the time that remains to him. This was true of one of our patients who lived several months after resection of an adenocarcinoma of the sigmoid which was found at the time of laparotomy to have metastasized to the liver and to distant lymph nodes.

Certain basic principles govern the surgical management of cancer of the large bowel. Foremost, it should be emphasized that operation is not an emergency except possibly in the case of obstruction. In the presence of obstruction the bowel must be decompressed before any radical or major operative procedure is attempted. Whether or not a preliminary proximal drainage should be done routinely in all cases, regardless of the presence of obstruction, the age, or condition of the

Postoperative Care—Fluids ordinarily are not given by mouth until gas has been expelled. In most cases, however, the patient can tolerate small amounts of water of room temperature after the first twenty-four hours. If a Miller-Abbott tube is in place, some fluid may be introduced through this tube. The bulk of fluids and nutrients are given parenterally in the form of glucose, saline, distilled water and amino acid solutions. Plasma and blood are given as needed to maintain proper chemical balance. Vitamin supplements, especially vitamin C which plays a role in wound healing, may be given with the infusions or by injection. Continuous suction siphonage is maintained through the Miller-Abbott tube for the first twenty-four hour postoperative period at least. Readily absorbable sulfonamide compounds like sulfathiazole and sulfadiazine are given until the temperature is normal and has remained so for forty-eight hours in order further to combat peritonitis and wound infection. They may be given with the parenteral fluids until such time as the patient can tolerate material by mouth. Penicillin and streptomycin may supplant these drugs when they are available for wider use. If the operative procedure ended in a colostomy, as in the case of an abdominoperineal resection, there is little need for the poorly absorbed sulfonamides, sulfathalidine and sulfasuxidine. If, however, the operative procedure involved suture of the bowel with retention of the involved segment in the peritoneal cavity, Poth³⁴ believes they should be given for twelve days postoperatively to control the intestinal bacterial flora. These, too, threaten to be replaced by streptomycin. Oxygen by mask or nasal catheter immediately after the operation will help avoid pulmonary complications, as will occasional whiffs of carbon dioxide, massage of the extremities, frequent change in position and the use of the anticoagulants, heparin and dicoumarol.

A word might be said here about the *care of a colostomy*. The poor reputation which colostomies have is the result of experience with those done for purely palliative reasons. If the primary tumor is removed and certain principles of care are observed, life with a colostomy is not the dread existence it is popularly conceived to be. After healing has occurred the patient should be taught to irrigate the colostomy regularly each day. After irrigation the area is cleansed and covered with a protective film of petrolatum gauze or a dry dressing and an abdominal support is applied. A protective paste of aluminum, zinc oxide ointment or a detergent such as alkyl sulfate in a bland base, may be coated over the skin should it become excoriated. With the use of a constipating type of diet and hydrophylic colloids, kaolin, and similar preparations, the irrigations may soon be stopped and a regular bowel habit developed. From four to six months is usually required before a colostomy functions most satisfactorily. Babcock² favors placing the colostomy in the perineum rather than the ab-

domen because in his experience less care is required, the situation is more like the natural one and better control is developed

Nonoperative Treatment—Malignant growths which are accessible through the proctosigmoidoscope may be destroyed by means of *surgical diathermy*, employing either electrocoagulation or fulguration. Strauss⁴¹ and Ferguson²¹ report favorable results with the former, and Buie¹² has been impressed with some results he has obtained with the latter method. However, the number of cases in which surgical diathermy may be employed is not great and the ultimate value of this form of treatment, especially as compared to other methods with which it must compete, is yet to be determined. *Radiation therapy* has a distinct place in the management of cancer of the large bowel. Radium is especially useful in those technically inoperable or in recurrent lesions of the lower bowel so situated as to be accessible for local implantation of radium seeds. Radon seeds may also be applied pre-operatively to reduce the size of a large growth and thereby permit a more conservative type of operation. Although the suitability of interstitial radiation is limited, external radiation may be more widely applied.⁶ Roentgen radiation is most useful when combined with radium, particularly in inoperable lesions or in individuals who refuse surgery. Other forms of nonoperative treatment have been employed in cases of malignancy of the large bowel, but none of them appear to have achieved any significant degree of success. These include the application of carbon dioxide snow, the intramuscular injection of colloidal metals, such as lead phosphate and selenide, copper and gold, the injection of a mixture of the toxins of *Streptococcus erysipclatis* and *Bacillus prodigiosus*, so-called Coley's fluid and, more recently, the administration of avidin, a protein present in egg-white which is capable of reducing the amount of biotin available for storage in neoplastic tissue.

The care of the patient with advanced inoperable cancer of the colon or rectum is a taxing problem. Numerous methods of alleviating pain are available and may be employed as needed. These include the use of opiates, cobra venom, the introduction of alcohol or ammonium sulfate into the subarachnoid space, local sympathetic nerve block and, in desperate cases, chordotomy. Rectal irrigation with warm 1:10,000 solution of potassium permanganate or physiological saline solution may help diminish rectal discharge. If bowel motions are frequent and troublesome, opiates may be given in sufficient amounts to paralyze the bowel. Liquid petrolatum or saline laxatives are of value to help overcome the threat of complete blockage in the presence of an obstructing lesion. Brandy or other alcoholic concoctions may stimulate a jaded appetite and food should be prepared and served in as attractive a manner as possible. An attempt should be made to keep the patient occupied writing, reading or otherwise en-

gaged with the various productive endeavors offered by the occupational therapist

PROGNOSIS

The average operative mortality throughout the United States at the present time in cases of cancer of the large bowel is in the neighborhood of 10 per cent. The rate is steadily being reduced, however, and many competent surgeons have already achieved remarkably low rates, especially for combined abdominoperineal resection for cancer of the rectum and rectosigmoid. In the group of twenty-one military patients I have followed, twelve were operated on and a resection accomplished with one immediate postoperative death, a mortality of 8.3 per cent.

With incomplete treatment, palliative treatment or no treatment whatsoever, patients with rectal cancer live an average of ten to eleven months after the diagnosis has been established. Under similar circumstances, patients with colonic cancer live an average of six months.⁴⁰ The bright note in prognosis is the fact that approximately half the patients with cancer of the colon or rectum who survive radical resection live for five years or more.^{14 15} The unfortunate thing is that the lesion proves to be resectable in only half the cases when the patient is first seen. The results following radiation therapy are conflicting. Five year survival rates have been reported which range from 18 per cent⁸ to 50 per cent.⁶ Electrocoagulation has still to be assessed, Strauss and his co-workers⁴² have reported a survival rate of over five years in 25 per cent of the cases they treated.

The outlook in malignant tumors of the large bowel seems much better than that for most other forms of internal cancer. As compared with cancer of the stomach, a disorder only slightly greater in frequency, the five year curability is at least three times as great. The progressive increase in operability rate and the concomitant decrease in mortality is resulting in a climbing survival rate and a greater total number of survivors. The problem remains largely that of early diagnosis. If there could be established a rigidly observed program of periodic health examinations which would include a digital exploration of the rectum, and if all discovered precursor lesions, especially adenomatous polyps, were destroyed as by fulguration, the toll of death from malignant tumors of the colon and the rectum would be appreciably reduced. The laity must be induced to seek medical attention much earlier than has hitherto been the case. Physicians in turn must be exhorted to apply freely and without procrastination those diagnostic procedures now at their command. Most important of all, a colon cancer awareness must be engendered in both the public and the members of the medical profession.

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DIAGNOSIS AND MANAGEMENT OF ULCERATIVE COLITIS

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THE term "ulcerative colitis" has been applied to a variety of unrelated conditions. Many diseases are characterized by the presence of ulcerative colonic lesions. Barger classifies ulcerative colitis according to etiologic types and emphasizes the necessity for an attempt to determine the specific etiologic factor in the individual case. Bockus defines ulcerative colitis as "a clinical syndrome ushered in with a suppurative, ulcerative inflammation of the colonic mucosa, with or without a recognizable initial specific bowel infection, but associated with a bacterial or toxic invasion of the bowel wall, conditioned by varying immunologic, allergic, nutritional and nervous phenomena."

ETIOLOGY

The relatively large numbers of soldiers returning to the United States from foreign service with a diagnosis of ulcerative colitis makes it incumbent on military and civilian medical personnel to entertain a clear conception of the probable etiologic factors in order to apply specific measures where indicated.

Much acrimonious debate centers about the etiologic relationship of *Barger's diplostreptococcus* in the most typical examples of ulcerative colitis. Barger's earlier case reports emphasized the primary etiologic importance of the diplostreptococcus in ulcerative colitis but subsequent reports, not only from Barger but from other investigators, cast some doubt on the validity of the earlier findings. At present, apart from Barger, the consensus relegates the diplostreptococcus at best to a relatively minor role as an etiologic factor in ulcerative colitis.

In 1936, Felson called attention to the role of *chronic bacillary dysentery* as an etiologic agent in ulcerative colitis and allied lesions. There is much in the present aspect of recently studied cases of bacillary dysentery in American troops returning from the Orient to substantiate Felson's concept. Many cases of acute bacillary dysentery merge into a chronic stage in which an ultimate diagnosis of ulcerative colitis is justified. Cases of colitis due to *Endamoeba histolytica* not infrequently become chronic and cannot be distinguished from other forms of ulcerative colitis by sigmoidoscopy alone. Whether the lesions of bacillary and amebic colitis are in themselves true evidences of early ulcerative colitis or whether or not they so debilitate the bowel

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that another form of ulcerative colitis supervenes, is a moot question. I myself believe that chronic bacillary and amebic disease of the large bowel are indistinguishable from so-called idiopathic ulcerative colitis. The importance of establishing a correct etiologic diagnosis is referable to the relatively good therapeutic response in the amebic variety, a response incomparably better than that noted in all the other varieties of ulcerative colitis.

Other less common forms of ulcerative colitis are due to *tuberculosis* and the *virus of venereal lymphogranuloma*. Tuberculous infection of the large bowel usually occurs secondary to small bowel involvement, and both are secondary to tuberculous lesions either in the lungs or elsewhere. Primary colonic tuberculosis is extremely rare. Recto-sigmoidal invasion by the virus of venereal lymphogranuloma is sufficiently characteristic in most cases to afford relatively easy recognition.

The lesions of the regional type of ulcerative colitis form a subgroup of the so-called "ileocolitis" group of cases. When Crohn first described terminal ileitis in 1932 it was believed that the lesion was limited to the terminal ileum. This chronic stenosing granulomatous type of lesion soon was reported in cases involving not only other portions of the ileum but various other portions of the small bowel either in contiguity or as skip areas. The disease also was present in the cecum and other portions of the large bowel. Initially, large bowel lesions of that type were regarded as secondary to ileal or other small bowel lesions. Soon, isolated involvement of segments of the right colon was noted and the term "right-sided colitis" became popular. Later, segmental involvement of any portion of the large colon was described. It was generally believed that involvement of the distal colon and rectum was a late phenomenon and occurred only subsequent to involvement of the colon elsewhere. That was in contradistinction to the typical lesions of so-called distal ulcerative colitis which originated in the rectosigmoid area and progressed orad. While there was much in the clinical behavior, gross pathologic specimens and therapeutic response to indicate that right-sided and distal colitis were separate entities, yet there were sufficient similarities to suggest that both conditions represented variants of the same pathological entity. I am in accord with the latter view and believe that an open mind should be maintained until sufficient evidence accumulates to differentiate the two conditions on the basis of etiology.

Andresen has called attention to the *allergic* character of certain cases of ulcerative colitis. Barger states that few will be impressed by the thought that allergy is a primary factor in ulcerative intestinal disease although allergy certainly occurs in many patients with ulcerative colitis. Barger likewise comments adversely on the role of nutritional deficiency as an important primary factor in ulcerative colitis.

When all diagnostic endeavors have been exhausted there will re-

main a not inconsiderable group of cases of ulcerative colitis in which the etiology remains obscure. In my experience most cases of ulcerative colitis fall into that group. The percentage of any observer's cases in that group will depend on the rigidity with which he measures his material with the etiologic yardstick. Unsupported evidence, surmise and stubbornness on the part of observers have contributed not a little to the present confusion regarding the etiology of ulcerative colitis.

The conflicting views of competent observers on the bacteriologic and parasitic origin of ulcerative colitis have invited attention to other etiologic factors among which are certain *psychogenic influences*. Careful clinical evaluation of isolated cases reveals many abnormal psychiatric and personality variants which seem to influence the course of the disease. No consistent behavior pattern has been described in ulcerative colitis but situational difficulties involving conflict not rarely influence the onset and course of the disease. The role of merely being a member of the armed forces, not to mention actual participation in battle, together with concern over home problems individually or in the aggregate, may constitute sufficient psychic provocation to initiate or prolong an attack of ulcerative colitis. The therapeutic implications are evident in the control of psychic influences engendered by warfare. Frequently the suggestion of probable separation from the military service initiates striking subjective and objective evidences of improvement in the course of the disease. The frequency of such a favorable therapeutic response lends support to the proponents of the psychogenic etiology of some cases of ulcerative colitis.

DIAGNOSIS

The variable clinical picture of ulcerative colitis demands a *careful anamnesis* in which is recorded the exact time of onset of the earliest symptoms with special reference to diarrhea and cramps, noting the initial character of the stools, the presence or absence of blood, pus and mucus and the duration of each, fever and leukocytosis. Many patients have hazy recollections of their earliest symptoms but careful questioning will elicit the important data in most instances. Frequently troops were in combat where hygienic facilities and laboratory equipment were primitive, in which cases important data may be missing. The geographical site of the onset may furnish an important etiologic clue. Were other members of his outfit similarly troubled? What treatment did he have initially and how effective was the treatment? It is surprising how easily the soldier remembers the terms emetine, carbarsone, "sulfaguanidine," bacillary and amebic dysentery." One soon learns that the terms "amebic and bacillary dysentery" are used in the Orient frequently without benefit of the microscope or culture media. One should like to know whether the diagnosis was made in the field or in a hospital in the latter case was it an

evacuation station or general hospital? Was the soldier treated by American or foreign physicians? Very important is the transmission of the earliest medical records of the patient. Unfortunately, in the chain of evacuation, important medical data may be missing or, at the best, fragmentary.

The subsequent course of the disease in respect to continued diarrhea and cramps, general systemic effects and the results of further study is important. A soldier may have had bacillary dysentery in one theater and amebic infestation in another. One may have cleared and the other continued in chronic form. A record of the earliest sigmoidoscopic examination may afford the most important etiologic clue. One should like to know something of the experience of the initial examiner. Unfortunately, lurid sigmoidoscopic examination reports may be submitted by inexperienced observers. The examiner should inquire particularly into the remote bowel history of the patient. Has he always had some intermittent diarrhea and constipation? What, if any, medical care had he received? The location of the home of the patient may suggest an etiologic agent. A detailed account of the character of any abdominal pain and its relation to bowel function should be noted.

The general *physical examination* apart from an appraisal of the nutritional state of the patient rarely affords any significant finding in ulcerative colitis. The presence of abdominal masses or any evidence of peritoneal irritation has a bearing on complications of ulcerative colitis.

The most important diagnostic procedure in ulcerative colitis is a properly performed *sigmoidoscopic examination* in the hands of someone familiar with the disease. One should be able to recognize the variations of normal mucosa, and the expected changes following a cleansing enema. The writer prefers to visualize a mucous membrane untraumatized even by a cleansing enema. One must not infer that any acute involvement of the rectosigmoid mucosa represents ulcerative colitis. In its earliest phase nonspecific acute ulcerative colitis presents a red friable mucosa which traumatizes easily. Somewhat later, application of a cotton swab to the mucosa reveals a faintly granular mucosa with multiple pin-point bleeding areas. Diffuse granular mucosa of varying degree is the most outstanding characteristic of a well developed ulcerative colitis. Subsequently the small granular pin-point areas may undergo hyperplasia of varying degree which in extreme cases may progress to the frank polyps quite common in late ulcerative colitis. The degree of bleeding seen on sigmoidoscopic examination is a rough index of the activity of the disease. One may see a granular mucosa quite free of active bleeding in quiescent chronic cases. Frank ulceration, in my experience, is a somewhat less common finding than the diffuse granular appearance previously described. Ulcers of varying size do occur and may become quite prominent.

Much of the surface may be plastered with a variable coating of thick mucopurulent material. If one could separate the various merging stages of ulcerative colitis into the clear-cut groups so succinctly described by others, he would find that it adds little to the clinical picture. In the late chronic stage when fibrosis of the bowel wall supervenes, a narrowed bowel lumen may be seen which at times presents a variable surface depending on the activity of the process. Ultimately all of the visible mucosa is so altered that it loses its normal appearance. In mild cases the mucosal involvement may be localized in a small area in the distal rectum or on the surface of one of the valves of Houston. However, if the disease is prolonged, one may expect extension of the involved area until all of the mucosa within reach of the sigmoidoscope is involved.

The preceding description is applicable to the sigmoidoscopic picture in the usual type of nonspecific ulcerative colitis. Certain features are helpful in instances where confusion may exist concerning the stage and etiology of a suspected case. Attention has been called to the fiery red mucosa of acute bacillary dysentery and the discrete undermined ulcers of typical amebic dysentery. In the more chronic stages of bacillary and amebic dysentery, mixed secondary infection with varying types of colon bacillus, staphylococcus and streptococcus organisms may so alter the appearance of the mucosa that the original character of the diseased mucosa is lost and a nonspecific appearance supervenes which is indistinguishable from typical ulcerative colitis. The demonstration of specific etiologic agents by smear or culture may afford the only clue to the original type of involvement. In many cases in which early competent studies have demonstrated the presence of specific agents, subsequent studies have failed to confirm those findings even in the presence of continued active colonic disease.

X-ray examination of the colon by *barium enema* outlines areas inaccessible to direct visual examination by the sigmoidoscope. Certain important features should be noted: the fuzzy character of acutely involved mucosa, polypoid changes in chronic cases, generalized irritability of the colon with loss of normal haustral markings, shortening and narrowing of the lumen and some estimation of the total extent of colon involved in the disease process. Roentgen studies of the small bowel with special attention to the terminal ileum may be required in extensive cases.

Reference has been made to the importance of laboratory procedures in the diagnosis of ulcerative colitis. Smears of the mucosa taken through the sigmoidoscope should be examined immediately microscopically for pus and motile and cystic forms of amebae. Cultures similarly obtained should be studied for organisms of the typhoid-dysentery group and amebae. A most important and frequently overlooked examination in chronic cases is the detection of motile amebae in the stools following a saline laxative. Schistosomiasis is common in

troops returning from certain areas but, while an important finding, is rarely a factor in ulcerative colitis itself

MANAGEMENT

Medical—1 The importance of evaluating psychosomatic influences in ulcerative colitis is reflected in the strikingly good therapeutic effects of expert *psychotherapy*. Regardless of other etiologic factors, psychotherapy is of paramount importance and in my own experience it, more than any other single factor, seems to initiate early improvement in instances in which clearly defined psychosomatic problems are resolved. The value of psychotherapy will vary with the type of patients and available therapeutic means. Returning soldiers present problems of infinite variety with reference to overseas experiences and local, economic, moral and social responsibilities. The physician, however, must not neglect other therapeutic aspects of the condition, particularly in instances in which specific etiologic factors are suspected.

2 The *diet* should consist of low roughage foods of high caloric value rich in proteins. Individual dietary idiosyncrasies must be recognized and adjusted. The addition of supplementary iron and vitamins is necessary particularly in debilitated patients with secondary anemia and evidences of avitaminosis. In cases of excessive diarrhea, the parenteral administration of vitamins should not be neglected. In severe cases, the parenteral administration of blood plasma and amino acids may be required until the diseased colon is sufficiently quiescent to tolerate adequate oral feeding.

3 *Specific Measures*—In cases in which *Endamoeba histolytica* is the primary factor, I prefer the use of emetine hydrochloride as an initial measure, prescribing 0.03 gm ($\frac{1}{2}$ grain) twice daily for not more than four to six days. Concurrently with the administration of emetine, carbarsone 0.25 gm ($3\frac{3}{4}$ grains) three times daily is given for seven days, followed by chiniofon 1 gm (15 grains) three times daily for seven days. Lastly, diodoquin 0.63 gm (9.6 grains) three times daily is given for seven days. At the conclusion of the above course, if cysts of *E. histolytica* are present in the stools the whole course is repeated. The chronicity of long-standing amebic infestation requires constant vigilance in the detection of recurrences. Patients with amebiasis may require specific treatment for years and some authorities claim that in a small percentage of cases special programs including retention enemas and the exhibition of other antiamebic drugs may be indicated. The use of sulfadiazine, alone or in conjunction with sulfaguanidine or sulfasuxidine, in cases of chronic bacillary dysentery is universal. Twelve or sixteen grams of sulfaguanidine or sulfasuxidine daily, divided into four doses, are prescribed over a ten day period. A second course may be used after a ten day rest period. It is my policy to use sulfaguanidine or sulfasuxidine in all cases of chronic

colitis in which an exposure to, or history of, bacillary dysentery may be elicited. The concomitant administration of sulfadiazine and either sulfaguanidine or sulfasuxidine enhances the expected favorable result by taking advantage of the general systemic and local colonic therapeutic effects of the sulfa group. The use of sulfa drugs in the control of secondary invaders in cases primarily due to the virus of lymphogranuloma venereum has received favorable mention. The use of small doses of sulfaguanidine or sulfasuxidine at repeated intervals in ambulatory cases of chronic ulcerative colitis deserves mention because of the excellent therapeutic response in some instances.

Surgical—The consensus of good medical judgment is not in favor of operative intervention in early uncomplicated ulcerative colitis, however, there is an accumulating mass of surgical opinion favoring early operation in cases of ulcerative colitis, utilizing a variety of ileostomies and colostomies devised to rest the diseased bowel. In such instances eventual colectomy is usually contemplated. Instances of acute bowel perforation, fistulous development and stenotic complications may require appropriate surgery. There are cases of ulcerative colitis in which heroic surgical management is indicated but the usual favorable result to be anticipated from an adequate medical regimen precludes the necessity of surgical measures. The earlier enthusiasm for colonic resection in cases of uncomplicated right-sided colitis has given way to a more conservative attitude, reserving surgery for complicated cases. In an instance in which surgery is contemplated in severe ulcerative colitis the case must be highly individualized and only a surgeon with a large experience in colonic surgery should be entrusted with the responsibility.

MECHANICAL INTESTINAL OBSTRUCTION FOLLOWING WAR WOUNDS OF THE ABDOMEN

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THE return of large numbers of wounded veterans to civilian life will increase the importance of certain pathologic conditions. These will be brought with increasing frequency to the attention of the general practitioner and the surgeon. One pathologic entity most surely to be encountered more frequently is mechanical intestinal obstruction. Never before have so many soldiers sustained abdominal wounds and survived to return to civilian life. Never before have so many young adults had injuries to, and multiple celiotomies performed on their peritoneal cavities. Army surgeons engaged in definitive abdominal surgery in military hospitals here in the United States have found that soldiers who have sustained abdominal wounds almost invariably have severe intra-abdominal adhesions, the predisposing factor for mechanical obstruction.

Incidence.—There have been, already, numerous instances of intestinal obstruction in Army general hospitals among the wounded returned to the United States.

The total incidence of obstruction among all patients with abdominal wounds admitted to Rhoads General Hospital during the past year for disposition is one in every 7.9 cases.

The incidence of mechanical obstruction as a result of abdominal wounds, both large and small bowel, requiring operative intervention on the Surgical Service at Rhoads General Hospital during the past year is one in every 18.5 cases.

These figures indicate that intestinal obstruction is a factor to be reckoned with in the future lives of these men. Since their future care and welfare, following their return to civilian life, will rest in the hands of the family practitioner, it is of the utmost importance that he be informed of the likelihood of this abdominal emergency.

Both large and small bowel obstruction has been encountered. The comparative incidence of the two in our series shows that small bowel obstruction occurs 3.5 times as frequently as large bowel obstruction.

Etiology.—The predisposing factor in obstruction, of course, is *abdominal traumatism*, leading to the development of severe intra-abdominal adhesions, angulation or other deformity of the intestine. Almost

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all the soldiers who have had abdominal wounds have had peritonitis of greater or less severity, and have also had complete exploration of their abdominal cavities with some attendant trauma in handling. Many have also had multiple resections of bowel and/or the establishment of a colostomy. It is the established rule in the Army Medical Corps that *wounds of the small intestine* may be closed by suture or injured segments of small bowel resected and anastomosed and the abdomen closed. *Wounds of the colon*, however, must be exteriorized, or sutured and a proximal obstructive colostomy established. This entails one or more additional celiotomies to close the colostomy. In the surgical treatment of nearly two hundred of these cases, we have come to know the extensive adhesions found in these abdomens.

Observation has also led us to recognize several predisposing factors in the actual onset of obstruction. The first of these is *prolonged travel*, such as transportation by train, motor vehicle or plane. This is illustrated by Case I in our series. The second factor is *submission of*

TABLE 1.—INCIDENCE OF INTESTINAL OBSTRUCTION OCCURRING BOTH HERE AND OVERSEAS IN PATIENTS ADMITTED TO GENERAL AND SEPTIC SURGICAL SECTIONS OF RHOADS GENERAL HOSPITAL DURING A TWELVE MONTH INTERVAL

		Per cent
Patients with abdominal wounds	221	
Small bowel injuries with subsequent complete obstruction	13	5.9
Small bowel injuries with subsequent partial obstruction	10	4.5
Large bowel injuries with subsequent complete obstruction	3	1.3
Large bowel injuries with subsequent partial obstruction	2	.9
Total cases of obstruction subsequent to battle wounds	28	12.6

the patient to a general anesthetic for any type of surgery, not necessarily involving the abdomen. To explain the second factor, we have developed the hypothesis that, following an abdominal wound and concomitant with the development of the adhesions, the intestine develops a set pattern of motility. As long as this pattern is maintained, the adhesions do not cause obstruction. However, when the patient is given a general anesthetic, peristalsis ceases. This inhibitory action of anesthetics, particularly barbiturates, on bowel motility has been amply discussed by Bisgard and Johnson,¹ McClure et al.² and Miller and Plant.³ We assume that, with the resumption of peristalsis, bowel motility starts off in a different pattern and, much as a train which has jumped the track, the intestine comes to grief in an entanglement of adhesions.

Pathology—The inflammation and peritonitis following an abdominal wound form adhesions, bands and membranous exudative sheets, which are instrumental in causing omental and intestinal entanglements.

In small bowel obstruction, all manner of kinks, torsion and internal herniations may be encountered. The most common forms are the "fixed kink," the "closed loop" or "double fixed kink," and the "traction obstruction" with an adhesive band at the apex of a loop of gut acting as an axis about which a volvulus can take place.

In colonic obstruction the most common finding is an inadequate lumen, often resulting from a Mikulicz type of colostomy closure (see Case IV). Another interesting type of colonic obstruction is illustrated by Case V in which the obstruction was internal, due to a marked hypertrophy of one side of the crushed spur of colon wall following a Mikulicz closure of colostomy. This formed an obstructing tumor mass which produced intussusception and occlusion.

The pathologic physiology of intestinal obstruction has been covered by many excellent reports in the recent literature, by Cooper,⁴ Donaldson et al.,⁵ Harkins⁶ and Gius and Peterson.⁷ It is not within the scope of this discussion to review this at length. However, certain aspects should be briefly reviewed for their later bearing on treatment.

The changes which occur once intestinal obstruction is complete fall into two groups. The first group consists of the shock syndrome, which frequently follows obstruction. Moon and Morgan⁸ and Fine and co-workers⁹ have shown that there is a definite loss of circulating plasma volume following intestinal obstruction. Laufman and Freed¹⁰ and Heuer and Andruss¹¹ have investigated the vasodepressor effect of the transudate from obstructed intestine as an explanation of this shock. The second group of changes which follows obstruction are those related to the viability of the bowel. Intestinal distention leads to distention necrosis. This in turn leads to perforation and peritonitis. Strangulation of the blood supply likewise results in perforation and peritonitis. Gatch¹² has stated that the bowel can survive no more than six hours of complete anemia.

These two groups of sequelae account for the morbidity in intestinal obstruction, and decisions as to treatment and evaluation of each case must be taken with their recognition and prevention in mind.

Diagnosis—Small Bowel Obstruction—As in many other surgical conditions, the so-called "textbook picture" is too frequently thought of in considering small intestinal obstruction. Such advanced signs as the stepladder effect on both inspection and x-ray examination and "fecal vomiting" are too often emphasized.

The most common symptoms in small bowel obstruction are the onset of increasingly severe, intermittent, crampy, abdominal pains, accompanied by nausea and usually by vomiting. These symptoms, accompanied by the presence of one or more abdominal scars and a history of a war wound of the abdomen or a thoraco-abdominal wound, should immediately alert the physician for the diagnosis of intestinal obstruction. Pain on palpation over the obstructed loop is

frequently present Unless perforation has already resulted or is imminent, marked abdominal rigidity is usually not present A thoraco-abdominal wound may be misleading, since the only scar may be on the chest wall The temperature is usually normal in early stages, but tachycardia may be present

Auscultation of the abdomen is still important It is as valuable to the diagnosis of surgical disease of the abdomen as auscultation of the chest is to the diagnosis of thoracic disease At the onset of obstruction, violent intestinal peristalsis can be heard Later the abdomen is more quiet, and the cracked bell sound is heard

"Clinical" distention in small bowel obstruction is almost never present If present, it is usually mild in degree unless the obstruction is low in the ileum

Roentgenographic examination is important Gius and Peterson⁷ state that x-ray evidence of obstruction is positive in over 80 per cent of the cases Once again it should be emphasized that the stepladder effect should not be used as a criterion We agree with Solis-Cohen and Levine¹³ that the visible distention of an isolated loop or loops of small bowel indicate an obstruction which usually requires surgical intervention It has been stated that the herringbone pattern due to illumination of the valvulae conniventes by collected gas is a picture visible almost solely in mechanical obstruction

Early, the white blood cell count is normal or only slightly elevated A rapid or high elevation of the white cell count is a sign of impaired intestinal viability, and indicates an extreme emergency The hematocrit and Scudder's falling drop test are of value in showing hemoconcentration and decreased circulating plasma volume These indicate the need for plasma or blood transfusions

Large Bowel Obstruction—The symptoms of large bowel obstruction develop more slowly and are more mild in nature The patient complains of mild abdominal cramps, particularly after meals, abdominal fullness, and often nausea Constipation precedes the inability to pass stool or flatus A history of a closure of colostomy is important Occasionally the onset is more rapid with more cramping, vomiting and marked distention No relief will be obtained with enemas The rectum is usually empty Occasionally, if either volvulus or intussusception of the colon complicates the picture, blood or blood and mucus will be passed

A flat plate of the abdomen will show marked distention of the colon proximal to the point of obstruction and, in addition, may show dilated small bowel This shows that the process is of longer standing and is complete It also indicates that the patient is in poorer condition Skiodin enema is of value in localizing the exact point of obstruction In these cases the leukocyte count is usually not elevated unless the patient has been vomiting protractedly or has a volvulus or intussusception The state of nutrition may be poor There may

be a moderate anemia. The determination of a patient's chlorides and plasma protein is important as guides to treatment.

TREATMENT

A review of the current literature reveals that, since the introduction of the Miller-Abbott tube in 1938, a definite trend toward alert observation has taken place. Although we would definitely deny the charge of seeking needless surgery, we feel that prolonged observation has very little or no part in the treatment of complete mechanical intestinal obstruction following abdominal war wounds. We believe that an early celiotomy offers the most satisfactory means of removing the cause of obstruction and saving the patient's life.

The basis of all present-day conservative therapy is suction decompression by means of a Miller-Abbott tube. Its use in treatment of intestinal obstruction was first advocated by Abbott and Johnson¹⁴ in 1938. Since then, many others have reported favorably on its use. We feel that the Miller-Abbott tube is of definite value in the treatment of inhibition ileus and in incomplete small bowel mechanical obstruction, but we are opposed to its use in complete obstruction following abdominal war wounds. In our own experience, results from its use were definitely not encouraging. Even the greatest advocates of suction decompression admit that its use in unsuitable cases is veritable expectans mortem treatment.

Gius and Peterson⁷ state as *absolute contraindications to the use of the Miller-Abbott tube* the following: (1) Use of the Miller-Abbott tube with the idea of completely decompressing the completely obstructed large bowel. (2) Its use in cases of strangulated obstruction or mesenteric vascular occlusion. The *criteria of intestinal strangulation* are: (1) A history of abdominal pain of rapid onset which persists between periods of cramplike exacerbation. (2) Persistent, retching vomiting. (3) Associated localized tenderness, spasm, or palpable tender abdominal mass. (4) Persistent tachycardia and leukocytosis after restoration of the fluid balance.

It is generally stated that strangulation or marked interference with blood supply is a factor in 10 per cent or less of all cases of intestinal obstruction. However, in our experience with obstruction following abdominal war wounds, the incidence is much higher. This is one reason why we are not in favor of the routine use of a Miller-Abbott tube.

The use of the Miller-Abbott tube is, at best, difficult and time-consuming, although Abbott has recently introduced a stylet for its rapid insertion. In the hands of the occasional user, twelve hours' delay is not unusual for its successful passage. This lengthy delay in cases with obstruction from abdominal war wounds may be fatal. We further feel that the symptomatic relief afforded to most patients may lull the occasional user into a sense of false security.

We believe that the following treatment in *small bowel mechanical obstruction* is safe, effective and productive of lowest mortality and morbidity. As soon as the diagnosis is established by means of positive physical findings and x-ray evidence of a dilated loop, Wangenstein duodenal drainage is started. Estimation and correction of the fluid and electrolyte balance are carried out as rapidly as possible. A celiotomy is then performed without further delay. Usually the point of obstruction is readily found after the abdomen is opened. When released, the bowel is seen to decompress rapidly and strangulated areas regain their normal color. However, when multiple areas of obstruction are present or suspected, the entire small bowel is gently inspected and all adhesions freed. All possible raw surfaces are peritonealized. When too extensive damage to a loop is noted, resection and anastomosis are accomplished.

Postoperatively, Wangenstein suction is continued as indicated. This period usually lasts at least forty-eight hours. Penicillin and sulfadiazine are given in adequate amounts. Prostigmine is administered for at least five to seven days postoperatively. A 12000 strength is used, starting with one ampule every three hours from the first day. Daily dosage is gradually decreased. The fluid and electrolyte balance are maintained. Amino acids are given parenterally until the patient is able to take an adequate protein intake by mouth. Adequate amounts of ascorbic acid and B complex vitamins are administered.

The treatment of *complete obstruction of the colon* is surgical. As soon as the diagnosis is established, duodenal drainage is instituted. The patient's fluid balance and electrolyte balance are corrected and maintained. Blood or plasma is administered intravenously as indicated. If the obstruction is complete, sulfadiazine is administered intravenously. When these measures have been accomplished, celiotomy is performed. The point of obstruction is located. In our experience it has usually been possible to do a primary resection and end-to-end anastomosis. This is accomplished by an aseptic technic, using a Furniss clamp. Primary end-to-end anastomosis of the colon has been possible in most of our cases. However, when there is not sufficient bowel to permit this, or when it is not necessary, we have found it possible frequently to straighten out an angulation or correct a narrowing of the lumen by longitudinal incision of the bowel and transverse closure.

When the colonic obstruction is not quite complete, we have in several cases been able to delay operation sufficiently long to allow for preparation of the bowel with sulfaguanidine or sulfasuxidine. In these cases, we have limited the oral intake to fluids. Heavy doses of sulfaguanidine have been administered orally. The fluid and electrolyte balances are maintained at normal levels. Parenteral amino acids are administered. This regimen is maintained if possible for a period of at least five to seven days, after which celiotomy is performed and

an open resection and end-to-end anastomosis of the colon accomplished Sulfadiazine is administered postoperatively. In our series, none of the cases treated in this manner have had an unsuccessful result or a postoperative peritoneal infection.

REPORT OF CASES

CASE 1.—This soldier, a private aged 30 years, was wounded in action in Germany by a high explosive shell fragment on March 12, 1945. At operation shortly after injury a severe excavating wound of the left lumbar region with marked loss of substance of the lateral abdominal wall was noted. A débridement was performed. In the opinion of the surgeon the peritoneal cavity was not in

TABLE 2.—RESULTS OF TREATMENT OF CASES OF ACTUAL OBSTRUCTION AT RHOADS GENERAL HOSPITAL

	Num ber of Cases	X ray Findings Positive	Suction Decom- pression Used Proper atively	Cases Requiring Emer- gency Operation	Obstruc- tion Proved at a Sub- sequent Celi- otomy	Evidence of Impaired Blood Supply to Intestine	Results of Treat- ment Number Recov- ered
Small bowel obstruction, complete	8	6	2	8		6	8
Small bowel obstruction, incomplete	4	3	4	0	3		4
Large bowel obstruction, complete	3	3	3	3		0	3
Large bowel obstruction, incomplete	2	2	1	0	2	0	2

Recovery was 100 per cent in all groups.

involved. The course was stormy for eight days, when rupture of a fecal abscess through the wound in the flank occurred spontaneously. Examination revealed a destruction of the apex of the splenic flexure. On the following day a proximal transverse colostomy was performed. The patient improved.

Twenty-eight days after injury the soldier was evacuated by air to the United States and admitted to Rhoads General Hospital on April 9, 1945. On the night of admission he complained of exhaustion, nausea and moderate cramplike abdominal discomfort. His colostomy had not functioned for twenty-four hours. Following the instillation of oil into the proximal loop of his colostomy he had a copious evacuation and all symptoms disappeared.

At 1:00 P.M. on the following day the patient again complained of an increasingly severe, cramplike, abdominal pain. This was followed by nausea and vomiting and very slight abdominal distention. Tenderness on palpation was noted in the left upper quadrant. The white blood count, taken two hours after

the onset of the symptoms, was 16,500, with 69 per cent polymorphonuclear leukocytes. The sedimentation rate was 44 mm per hour. Total serum protein was 5.85 gm per 100 cc. The hematocrit was 31 mm. A flat plate of the abdomen showed several markedly distended loops of small bowel.

Wangensteen duodenal suction was started. An intravenous infusion of 5 per cent glucose in normal saline was administered. When the pain and distention increased, the patient was scheduled for operation at 7:30 P.M. Ten minutes before going to the operating room he gagged on the nasal suction tube. The resulting increase in intra-abdominal pressure caused the evisceration of several loops of small intestine through the large wound in the left flank, which had been sealed off by the traumatic colostomy of the splenic flexure.

Celiotomy was performed immediately through a right paramedian incision. Three markedly dilated loops of lower jejunum were found, bound in a dense inflammatory mass in the left upper quadrant. One loop showed marked discoloration. These were freed and the obstructed bowel was immediately decompressed. The color of the strangulated loop returned to normal. The eviscerated small bowel was replaced. The flank defect was too large to close. The abdominal contents were contained within the peritoneal cavity by a gauze pack sutured into the defect by through-and-through tension sutures. The abdominal wound was closed. The patient received 500 cc of blood during the operation and 1000 cc of 5 per cent glucose in normal saline, plus 500 cc of plasma, on return to the ward.

The postoperative course was smooth and recovery was satisfactory.

CASE II—This soldier, aged 20 years, was struck by a .30 caliber, armor-piercing bullet, which first hit a walkie-talkie he was carrying and carried part of it into his abdomen. The wound was incurred March 29, 1945 in Germany. At operation in the field hospital it was found that the bullet had entered the abdomen through the left hypochondrium and had made its exit through the left flank, producing almost complete destruction of the splenic flexure of the colon and laceration of the left kidney. The splenic flexure was resected and a double-barreled colostomy established. The left kidney was sutured and the perirenal area drained. The patient developed a left-sided hemothorax, which was relieved by thoracentesis. A profuse purulent exudate soon began to drain from the wound of entrance and also from the perirenal wound. His condition was poor. He was transferred by plane to Rhoads General Hospital, twenty-five days after his wound was received.

On admission the patient was acutely ill, emaciated and showed marked sepsis. He complained of pain and marked tenderness over the lower sternum and lower left hypochondrium. He had a painful, nonproductive cough, the abdomen was scaphoid. A profuse purulent exudate was present in the upper angle of the abdominal wound and in the perirenal wound in the left flank. A well-functioning, double-barreled colostomy was present in the left lower quadrant. X-ray of the chest showed an old atelectasis of the left lower lobe.

On May 1, 1945 a diagnosis of left perinephric abscess was made. Under sodium pentothal anesthesia an incision was performed and pus evacuated, together with a black, plastic, foreign body from the walkie-talkie. The wound was picked open.

The patient made a slow recovery from operation. A pneumonitis, superimposed on his old atelectasis, developed. Intermittent nausea and vomiting and slight distention appeared, which was interpreted as inhibition ileus and suction decompression was begun. After forty-eight hours the patient improved. He was treated with large doses of penicillin and intravenous fluids. Suction decompression was discontinued. At the end of ten days, however, he again complained of intermittent nausea. Within twenty-four hours he developed acute, intermittent, cranialike abdominal pain, vomiting, a visible tender mass extending from the

right lower into the left upper quadrant and a cracked bell sound on auscultation.

A ray showed a markedly distended loop of small bowel. The patient's white blood count was 18000. A diagnosis of strangulation obstruction was made and celiotomy was performed under spinal anesthesia. A traction torsion obstruction of the upper ileum was found due to an adhesive band in the left upper quadrant. This was accompanied by marked discoloration of the bowel. The obstruction was released with resultant decompression of the bowel and return of circulation. The abdomen was closed in layers without drainage. The patient made a satisfactory postoperative convalescence.

CASE III.—This man, a private first class aged 25 years, sustained a penetrating wound of the thorax and abdomen on October 2 1944 in Germany. A thoraco-abdominal operation was performed four hours later and revealed a laceration of the left leaf of the diaphragm and a ruptured spleen. The spleen was removed and the diaphragm sutured by transpleural approach.

The patient was evacuated to the United States and admitted to Rhoads General Hospital on January 17 1945. His wounds were healed and his general condition was satisfactory except for a postoperative ventral hernia in the left upper quadrant. He complained of occasional attacks of recurrent pain and tenderness in the left upper quadrant. He gained in weight and strength, and repair of his ventral hernia was contemplated.

On March 5, 1945 at 9:30 P.M., he suddenly developed severe, cramplike abdominal pain, most severe in the left upper quadrant. His temperature was 98.2 F. There was no abdominal distention or rigidity. Slight generalized tenderness and hyperactive peristalsis were noted. He was treated by a suction decompression and in two hours experienced complete relief. He passed large amounts of flatus.

Eight hours later the patient again had severe cramping pain and showed slight distention. Marked tenderness was present in the left upper quadrant. A ray showed several markedly dilated loops of small intestine. His white blood count was 9500. Because of the progression of the symptoms despite suction decompression, a celiotomy was decided upon. This was performed twenty-one hours after the onset of symptoms. Under spinal anesthesia the abdomen was opened through an upper right paramedian incision. A large amount of peritoneal transudate was found. A closed loop obstruction of the high jejunum, resulting from adhesions in the left upper quadrant, was found and released. The patient had a stormy postoperative course necessitating Wangensteen suction for five days, but eventually made a complete recovery and later uneventfully underwent repair of his ventral hernia.

CASE IV.—A sergeant, aged 28 years, sustained a penetrating wound of the abdomen in Italy on February 4 1944. A celiotomy performed at a field hospital through a left subcostal incision revealed multiple perforations of the jejunum and laceration of the splenic flexure of the colon. The jejunal perforations were sutured and the laceration of the colon exteriorized as a colostomy. A subdiaphragmatic abscess was drained through a posterior incision. The colostomy functioned satisfactorily and while the patient was still recovering it was closed on April 18 1945 by a modified Mikulicz technic.

Because of persistent drainage from the incision to the right of the umbilicus, the patient was returned to the United States and admitted to Rhoads General Hospital on August 5 1945.

Examination revealed a left subcostal fistula and a draining sinus in the left costovertebral angle. At this time the patient was in satisfactory condition. X rays showed an area of cloudiness at the end of the left eleventh rib. This was removed on November 10 1945. The fistula healed completely.

In December, 1944 the patient began to complain of recurrent attacks of abdominal cramps and a sensation of upper abdominal fullness after meals. A barium enema showed a markedly angulated spur of colon with narrowed lumen attached to the anterior abdominal wall at the site of the colostomy closure. Operation was advised and this time the soldier refused. However, his symptoms became progressively worse. He limited his own diet to fluids, but nausea, vomiting and distention set in.

On January 4, 1945, under general anesthesia, a celiotomy was performed. The spur of the transverse colon was freed from the anterior abdominal wall. A plastic repair of the angulation was performed. The limbs of the spur were separated. The patient made an uneventful recovery and was symptom-free.

CASE V—This soldier, a private aged 32 years, sustained a perforating wound of the abdomen on December 7, 1944. A celiotomy performed one hour after injury revealed a perforation of the descending colon and a severe laceration of the left kidney. A transperitoneal nephrectomy was performed and the colon perforation exteriorized as a colostomy. The soldier made an uneventful recovery and for seven weeks, during which time the colostomy functioned, remained well. His colostomy was then closed by the Mikulicz technic. Three weeks later an abscess at the site of closure was incised and drained. Following this episode, diarrhea developed and still later a mucoid discharge was noted. Finally, just before evacuation to the United States, the diarrhea became bloody.

On admission to Rhoads General Hospital on April 14, 1945, the patient complained of continuous generalized cramplike abdominal pain and recurrent stabbing pain in the left upper quadrant, just above the site of colostomy closure. He was constantly nauseated and had had nothing by mouth for the past week. He was having 15 to 20 daily evacuations per rectum, consisting of nothing but blood and mucus. Examination revealed no distention but the entire colon was palpable to the mid-descending colon. There was marked tenderness over the mid-left abdomen.

The patient showed a moderate anemia. His red blood cell count was 3,700,000, with a white cell count of 11,500. A barium enema showed a mass in the mid-descending colon with intussusception at the site of obstruction. For ten days the patient was treated with intravenous fluids containing parenteral amino acids, transfused, and given sulfaguanidine orally.

A celiotomy was then performed. A large obstructing pedunculated tumor at the site of colostomy closure was noted. This was removed by resecting 14 cm of colon and performing an end-to-end anastomosis. The abdomen was closed without drainage. The patient made an uneventful recovery. The pathologic diagnosis on the tumor was given as a leiomyoma. It appeared to have developed from a hypertrophy of one side of the spur cut before closure of the colostomy.

SUMMARY

1 In World War II, many more soldiers than ever before who sustained abdominal wounds with fecal contamination have survived to return to civilian life. The incidence of severe intra-abdominal adhesions in these men is high. In a series of 221 abdominal wounds observed at Rhoads General Hospital, the incidence of intestinal obstruction was 12.6 per cent. This points to a greater incidence among returning veterans than normally encountered in civilians before the war. It is important that the civilian physician be informed of this and be prepared to make the diagnosis early.

2 All conceivable types of small bowel obstruction are to be found, including fixed kinks, double closed loops, traction volvulus, and internal herniation. Large bowel obstruction is usually due to inadequate lumen, resulting in most cases from a Mikulicz type of colostomy closure or inflammatory bands.

3 Diagnosis can be made on the following points: (a) a history of an abdominal war wound, (b) one or more operative scars on the abdomen, (c) a history of rapid onset of crampy abdominal pain with nausea and vomiting. There may be localized abdominal tenderness. (d) A flat plate of the abdomen will reveal one or more dilated loops of small intestine. In colonic obstruction the onset is gradual and the crampy pain is less severe and usually follows meals. X-ray examination shows a distended colon.

4 Treatment should consist of early operation and release of the obstruction in small bowel occlusion. We do not favor the routine use of the Miller-Abbott tube because of the high incidence of strangulation in these cases. The delay entailed in its insertion by the occasional user may be fatal. Its use in our hands has not been satisfactory. Colonic obstruction is treated by decompression, correction of fluid and electrolyte balance, and one-stage resection and anastomosis of the bowel by aseptic technique.

THE PROBLEM OF NUTRITION IN THE TREATMENT OF THE PROLONGED HOSPITALIZED PATIENT

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My remarks will deal with a subject the scientific understanding of which is gaining rapidly on the one hand while the general clinical application of this knowledge lags far behind on the other. I speak of the maintenance of the nutritional equilibrium of chronically ill patients. Far back in history students of medicine were taught according to ritual to bleed, sweat, purge and starve their patients. Prior to the twentieth century, there was little else, in an active way, that they could do. The modern era has relegated one of these pernicious practices—bleeding—to its proper place. The efforts to relieve physical illness and mental distress by purging are still widely practiced. Rooted in archaic and primitive beliefs rather than in physiology and pathology, this evil hangs on. However, the far reaching effect which purgation has in disturbing the water balance particularly in surgical and acutely ill and dehydrated patients is receiving increasing consideration. Shortly, this practice should follow that of bleeding down the avenue of relative disuse. It is on its way. Not so much progress has been made with starvation. The custom of prescribing starvation as a therapeutic measure in the treatment for acute febrile and surgical illnesses is still widespread. In the more learned circles starvation is not prescribed but is permitted. The results are much the same though the dignity of the procedure has suffered.

There are nearly two score of identified substances which the human organism must extract from his environment and take into itself if it is to function properly or survive. Lusk ably defined starvation as "the deprivation of an organism of any or all of the elements necessary to its nutrition." Deficient intake of any of the necessary food components represents undernutrition. A patient may be overweight and yet be undernourished in respect to certain food factors.

The nutritional status of an individual can only be summed up accurately by correlating the exact intake of the various food factors with the chemical analysis of the body fluids, notably the blood, and the quantitative analysis of the excreta be it urine feces vomitus or discharge of exudates or serous fluids. In the past, the body weight has been the indicator of the state of the nutrition of an individual. The body weight is a reliable index in this respect in the normal individual ingesting a normal diet and partaking of normal activities. It

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is not a reliable index of the state of nutrition of the bedfast, chronically ill or injured patient. In fact, changes of body weight may be grossly misleading. The undernourished patient with hypoalbuminemia may gain in weight from increasing fluid retention while his state of nutrition is deteriorating. Also, the same patient may enjoy his first improvement concomitant with a loss of body weight and fluid. Alterations in weight of from 6 to 10 pounds may ensue as the results of shifts in water balance and be quite undetectable to the eye.

In the first stage of undernutrition there is an indiscernible *tissue depletion* occurring when an amount of the nutritive factor sufficient to meet the organism's needs fails to reach the internal environment of the individual. At some stage in this depletion not enough of the nutritive factors are present to carry on normal biochemical processes in which they are involved and there develops a *biochemical lesion* detectable by biochemical analysis. Finally the depletion, progressing unchecked, accounts for the third phase which is that of the *anatomical lesion*—for example, the swelling of recent intestinal anastomoses, dermatitis, glossitis, cheilosis, and possibly the decubitus ulcer.

Mulholland and Co Tui* attribute decubitus ulcers to local pressure and to tissues impaired in vitality as a result of protein deficiency. In thirty-five random cases of bed sores they found the plasma protein concentration to be invariably below the lower borders of normal. This represents a tissue depletion of great magnitude. In well controlled studies of eight cases there was improvement in the general condition, gain in body weight, a rise in plasma protein and healing of the ulcers when the nitrogen balance was reversed from a negative to positive balance.

The anatomic lesions of undernutrition are depicted in the skin, eyes, oral cavity, nervous system and skeletal structure according to the respective deficiencies. These combined lesions—tissue depletion, the biochemical and the anatomical lesions—are all present in the advanced nutritional disorders. The stage was set for this abnormal clinical state with the onset of the predisposing illness or injury. The paraplegic, the bedfast and the convalescent patients are susceptible subjects. They are most likely to develop disturbances in nutrition and subsequent complications unless their *plight* is understood and this understanding is acted upon promptly and continuously until the need for special consideration no longer exists.

The nutritional disturbance may never develop to the stage where gross anatomic changes occur and yet it is probable that wound healing, resistance to infection and the feeling of well-being are interfered with. Clinicians too often have their sights set on anatomical changes as indications of deficiencies. This is a late stage and is the result of prolonged deficiencies. Much of our knowledge about dis-

* Mulholland, J. H., Co Tui, Wright, A. M., Vinci, V. and Shafiroff, B. *Ann Surg.*, 118(6) 1015-1023, 1943.

turbance of nutrition is based on total withdrawal of food factors from animals and little attention, until very recently, has been given to relative deficiencies over long periods

If normal nutrition is to be maintained attention must be focused on what the patient actually ingests and to acquaint ourselves with what it adds up to in terms of nutritional components I am sure I need not remind you that it is somewhat of a research problem in itself to find out what patients actually eat. I am not referring to the desperately ill but rather to the chronically ill patient—the paraplegic for example. The diet in treating the acutely ill patient with hepatitis became a matter of life and death and we were forced to have the meals and any left-overs weighed before sufficient attention was attracted to the imperative need of adequate intake. The same is true of chronically ill patients. The difference between the weight of food given to the patient and the weight of the food left uneaten should be checked when circumstances predispose to undernutrition. It is significant how frequently and how far these patients are off the nutritional beam. In short episodes this may be of little moment but in the paraplegic and in the patient with wound healing going on this subject assumes great importance. It is important not to overlook the nutritional background upon which the disorder has flourished or upon which a predisposition to further complications hangs. *I know of no therapeutically effective measure which is more often disregarded than that of maintaining a positive nutritional balance during the course of chronic and acute illnesses.* We, as clinicians, are guilty in this respect and I have an idea that the sins of the surgeons are no less scarlet in this matter.

Protein requirement deserves special consideration. If the energy expenditure exceeds the caloric intake the body protein is sacrificed and what is usually considered an adequate protein intake is not sufficient to prevent a deficit developing. Protein metabolism is spared by a high caloric intake and protein deficits can rarely be made up for more than short periods by giving large amounts of protein unless the total caloric intake is sufficient to prevent loss of tissue mass. Failure of absorption of food from one cause or another or increased demands as in pregnancy lactation, wound healing, rapid growth and disease magnify potentialities for nutritional deficiencies. Barr and his co-workers at Cornell have observed that a negative protein balance ensued when presumably normal conscientious objectors were confined to bed. The increased loss of nitrogen was most marked after the fifth day. Also there was a marked increase in the excretion of calcium and the pH of the urine tended to swing toward alkalinity enhancing the likelihood of calculi formation.

In civilian life the patient is discharged from hospitals when the acute phase of the illness is over. In most cases this is fortunate as they can have their individual wishes concerning diet catered to at home. This means that in all but the exceptional case adequate caloric intake

will be provided. This is, without doubt, the most important aspect of diet in general. Adequate caloric intake not only spares protein metabolism, it prevents abnormal demands on special food factors, notably vitamins, and it is much more likely to afford adequate intake of vitamins and minerals than is a low caloric intake.

The period of hospitalization for the Army patient covers not only the acute illness but convalescence which sometimes is prolonged indefinitely as in the case of the paraplegic. Unless special interest and effort provide an answer to the individual's wishes regarding food these patients, and patients from boarding houses and institutions, are more likely to become undernourished in one or another aspect than are patients discharged to their homes.

A patient seen *four* weeks ago, a paraplegic, had been admitted to one of our hospitals in January, 1945. He was well developed and appeared well nourished at that time but had decubitus ulcers of the heel, scrotum and knees. His blood count on admission was normal but subsequent counts revealed a gradual development of a hypochromic microcytic anemia. The total protein content of the plasma was normal with a satisfactory A/G ratio when first determined but subsequent determinations revealed a decline in the total protein and especially in the albumin fraction until on September 15 the albumin was 2.8 and the globulin 2.5 making a total protein of 5.3.

Clinically, anorexia became a problem, and as the months went by evidences of an avitaminosis became apparent. In August edema and ascites developed. The hazards attending his condition were being intensified by the loss of protein in the discharge from the decubitus ulcers.

Multiple transfusions of whole blood and two administrations of plasma between May 29 and September 14 failed to prevent deterioration of his clinical condition. On September 10 a diet estimated to contain 140 gm of protein, 400 gm of carbohydrate and 70 gm of fat was prescribed. Vitamin therapy was vigorously pushed and liver extract was given. On September 24 when I first saw the patient his appetite had improved, the evidences of avitaminosis had practically disappeared but the outlook was still grave owing to the persistence and degree of the ascites and the extent of the decubitus ulcers. On September 25, 100 gm of concentrated human albumin were given, on the 27th and 29th 75 gm were given, and the protein intake was increased. An intake of 300 gm daily was aimed at but only 162, 160, 182, 170 and 108 gm were ingested on successive days. This was accomplished only with every possible consideration being given to this patient's diet. By September 29 all ascites and edema had disappeared and the patient's condition was much improved and he was taking his diet much better.

This case illustrates what can happen to chronically ill patients kept in hospitals over long periods. This patient ran the gamut of undernutrition from indiscernible tissue depletion to anatomical changes which seriously threatened life. He illustrates what can happen and what in my opinion is happening in varying degrees to chronically ill medical and surgical patients hospitalized over long periods of time. The ultimate good which can come of the appreciation of these possibilities, the understanding of the underlying metabolic changes and the carrying through of the necessary prophylactic and corrective measures are far reaching. This problem of undernutrition extends to

every medical and surgical ward and yet, I confess, it is probably the most neglected field of promise in medicine. This is understandable. The onset is insidious. Months and weeks lapse before objective evidences of disease are apparent but it is well known that somewhere in this interim the patients become poor surgical risks, predisposed subjects for complications which may steal all the attention of the physician unless he is alert to the problem as a whole.

Acute medical and surgical complications are likely to claim the attention of the internist and surgeon and unless planned consideration is given to nutritional aspects changes, more far-reaching than is generally realized occur to the detriment of the patient.

The prescribing of the diet offers no problem to those familiar with food values. I believe that the approximate values in terms of grams of protein, carbohydrate and of total calories should accompany the diet prescription for every patient considered to be a susceptible subject for undernutrition. The diet would not need to be weighed. An approximation of the values would suffice as a guide to the dietitian. Not until this precautionary individualization of the needs of the patient receiving prolonged hospital care is adopted will needless risk to their health be avoided. Recently, I saw two paraplegic patients in the same ward. One, I believed, should have a diet approximating 125 gm of protein, 400 gm. of carbohydrate and 3500 calories. For the other I recommended 300 gm of protein, 300 gm of carbohydrate and 3500 calories. The first was a well nourished active, healthy appearing soldier having a normal appetite. The second had no appetite and had edema, ascites, protein deficiency and several decubitus ulcers.

SAMPLE DIETS FOR HOSPITALIZED PATIENTS

- I. Emaciated patient with hypoalbuminemia, edema, ascites with an indolent wound, or decubitus ulcer
- | | |
|------------------------|---------|
| Protein 4 gm. per kg * | 280 gm. |
| Carbohydrate | 300 gm. |
| Calories, 50 per kg | 3500 |
| Vitamins | |

(Restrict salt temporarily)

Of normal weight (Example 70 kg)

- II Undernourished patient with indolent ulcers (no edema, ascites or hypoalbuminemia)
- | | |
|-------------------------|---------|
| Protein, 2.25 gm per kg | 192 gm |
| Carbohydrate | 350 gm. |
| Calories, 45 per kg. | 3100 |

* Of normal weight. (Example 70 kg)

- III Normally nourished active paraplegic patient
- | | |
|------------------------|---------|
| Protein 1.75 gm per kg | 122 gm |
| Carbohydrate | 400 gm. |
| Calories, 35 per kg | 2450 |

Of normal weight. (Example 70 kg)

To see that the patient actually eats the prescribed diet is the crux of this whole problem. The importance which the physician attaches

to the necessity of eating will influence the patient greatly. It will influence the dietitian, the nurse and ward attendant and it will improve the patient's nutritional status. Supplementary feedings should make up deficits. One hundred grams of powdered skimmed milk in 200 cc of water yields 34 gm of protein and 52 gm of carbohydrate. To this concentrated nourishment ice cream, puréed banana, and the like, may be added. The quantity of fluid need not be great. Forcing of fluids by mouth is rarely necessary or advisable. Fruit juices are better omitted until they can be taken in addition to the prescribed diet. The same is true of beer. Fluids of low food value because of their bulk have an unfavorable effect on the appetite.

Parenteral Feeding is a temporary and an emergency measure. It may be the only means of providing nourishment for short periods and as a supplementary measure it has great value but *its use should be dictated by necessity, not by convenience.*

The *Fluid Volume* should be adequate to prevent the volume of urine falling below 1000 cc in febrile patients and the specific gravity should not be above 1.020. From 2 to 10 liters of fluids, according to the degree of hydration, will be needed each twenty-four hours. When the patient is unable to take any fluid by mouth, 3000 cc or more, given parenterally, are indicated.

Salt. From 8 to 10 gm of salt per twenty-four hours are desirable. More is necessary if vomiting is a feature.

Glucose. One hundred grams of glucose are necessary to prevent gross ketosis. This amount should be considered a minimum but twice this, at least, is desirable while no food is taken by mouth. Glucose may be given subcutaneously but only in 5 per cent concentrations. A 10 per cent solution may be given intravenously at a rate of 9 cc (150 drops) per minute or a 15 per cent solution at a rate of 6 cc (or 100 drops) per minute. A small needle (22-26) will aid in preventing a venous thrombosis.

The combined administrations of glucose and salt or glucose and protein hydrolysate are permissible if the solutions are given slowly (5 cc per minute).

Protein. Protein may be provided in form of whole blood, plasma, concentrated human albumen, hydrolyzed protein or amino acids. For purposes of nutrition, casein hydrolysate and amino acids are more practicable than are the blood products. The administration of amino acids or casein hydrolysate equivalent to 100 grams of protein daily during the emergency is desirable. These preparations are usually administered in a 5 per cent solution combined with glucose. The rate of administration should not exceed 500 cc per hour (8 cc per minute).

Vitamins may be added to the fluids to be given parenterally to the malnourished patient. The daily amounts recommended are thiamine 10 mg, riboflavin 5 mg, niacin 20 mg, and ascorbic acid 100 mg.

(Solu-B Upjohn 5 cc. provides all but the ascorbic acid, which should be added separately)

Examples of parenteral nourishment recommended by the National Research Council in Convalescence and Rehabilitation Report No. 1 February 1, 1944, are as follows

'1 It is desired to provide a non-febrile patient who is unable to eat or drink, but is not vomiting nor sweating, and who has no large, exposed exuding surface, for one day with water, salt and enough glucose to prevent gross ketosis.

Water	1500 to 2000 cc
Salt	5 to 8 gm
Glucose	100 gm.

1000 to 1200 cc. of 10 per cent glucose and 500 to 800 cc. of normal saline will meet these requirements closely enough. The total amount selected should preferably be given in two equal installments.

"2 If there has been a large antecedent deficit of salt as a result of vomiting, sweating, or transudation, the proportions of salt may be increased. For example

Water	3000 cc.
Salt	27 gm.
Glucose	100 gm.

In this case 100 gm. of glucose or 200 cc. of 50 per cent glucose are added to 3 liters of normal saline and divided into two portions in the same manner

"3 To meet the requirements for the nutrition of a patient who will be unable to take any food or fluids for some days and therefore should receive a nutrient which will provide an adequate amount of some protein substitute.

Water	3000 cc
Casein hydrolysate	100 gm
Glucose	200 gm
Salt	10 gm.

This will require 2 liters of 5 per cent casein hydrolysate, 5 per cent glucose solution and 1 liter of 10 per cent of glucose solution, a total of 3000 cc. Since the casein hydrolysate is neutralized it will contain 5 gm of salt per liter or 10 gm. in two liters. Other convenient formulae can be devised by which the volume can be kept below 3000 cc. The selected amount of solution should be injected over a period of about four hours or preferably in two equal installments of two hours each. If the patient is given transfusions of whole blood or plasma, the amount of casein hydrolysate will be decreased."

There is a challenge in this problem of nutrition, especially in the paraplegic or other patients subjected to prolonged hospital

The success which has met the efforts to cope with this problem in this hospital is not to be considered lightly. Clinical impressions have been given abundant scientific support. There is no longer refuge in the complacent acceptance as inevitable of the disturbances in nutrition which, it is obvious, can now be prevented in all but the exceptional cases.

ROUND TABLE DISCUSSION ON PROBLEMS OF NUTRITION

COLONEL G. G. DUNCAN, MAJOR HELMUTH SPRINZ AND MAJOR A. KLEINMAN

COLONEL DUNCAN *Major Kleinman, in your experience at Halloran General Hospital, what was the incidence of malnutrition among paraplegic patients?*

MAJOR KLEINMAN Nearly all patients with paraplegia were malnourished on arrival at Halloran General Hospital. Of eighty-two patients surveyed, the average weight loss since the time of injury was 49.47 pounds. Only two patients had lost less than 20 pounds, twenty-six patients had lost between 20 and 40 pounds, thirty-one patients between 40 and 60 pounds, seventeen patients between 60 and 80 pounds, and four patients over 80 pounds. One patient had lost 100 pounds and another had lost 102 pounds.

COLONEL DUNCAN *Maybe Major Sprinz will comment on the special significance of this loss of weight?*

MAJOR SPRINZ An average weight loss of 50 pounds incurred in a few weeks' time is almost unheard of in civilian practice, and can only be compared with the weight loss in other very serious war injuries and burns, for instance, in a series of twenty-nine cases of serious orthopedic and abdominal injuries, we observed a weight loss averaging 48.5 pounds, the weight loss ranging from 30 to 71 pounds. Weight loss by itself is a very important, but not entirely reliable criterion of malnutrition. The evaluation of weight loss must be qualified by the knowledge of the fat stores of the patient prior to injury, and the knowledge of the amount of extracellular fluid in the patient. Loss of fat tissue does not necessarily mean malnutrition, as a matter of fact it may be beneficial. Loss of muscle and organ protein, on the other hand, is one of the most important manifestations of malnutrition. Protein metabolism is linked to water balance and loss of protein leads to an increase of extracellular fluid. In the seriously depleted soldiers some of the weight loss is hidden by the increase of extracellular fluid. This "hidden edema" may amount to many pounds.

COLONEL DUNCAN *What manifestations of malnutrition, other than weight loss, were observed in these patients, Major Kleinman?*

MAJOR KLEINMAN Visible nutritional edema was observed in only one case. The skin in most cases had lost turgor, was pale and dry. The muscle tone was greatly diminished. Only an occasional patient disclosed anatomical evidence of vitamin deficiency such as glossitis or cheilosis. No obvious case of beri-beri was seen.

COLONEL DUNCAN *Why were there so few cases of vitamin deficiency among this group of seriously depleted soldiers?*

MAJOR SPRINZ Vitamin deficiency diseases are exceedingly rare in the United States Army, and have only been observed by us in repatriated prisoners who were on a starvation diet for a prolonged period of time. Apparently, a much longer time interval is necessary for the clinical appearance of vitamin deficiency than the three months it takes for paraplegic patients to arrive at a hospital in the Zone of the Interior. In addition, we are very vitamin conscious, and vitamin supplements are probably the first ones given.

COLONEL DUNCAN *Major Kleinman, what do you consider were the factors which contributed to the malnutrition?*

MAJOR KLEINMAN The nature of the injury, i.e., the injury to the spinal cord resulting in paralysis, often combined with other serious injuries such as chest and abdominal wounds, led to a state of mental depression with aggravation of the already existing anorexia. Abdominal wounds with perforation of the hollow viscera, necessitating one or more operations on the alimentary tract, and residual enteric fistulas, obviously contributed to the malnutrition. Many patients arrived with infected and draining wounds. All of the paraplegic patients had persistent albuminuria, varying from a trace to 2+. Finally, urinary tract infection was universal in this group producing in most cases a low-grade febrile response. Many patients were subject to repeated episodes of chills, septic fever and sweats lasting from a day or two to a week or more. The cause of these bouts was nearly always a pyelonephritis, although occasionally other causes were present. In summary, the factors contributing to malnutrition were mental depression, type and multiplicity of injuries, decubitus ulcers, persistent albuminuria, and last, but by no means least, infection.

COLONEL DUNCAN *Is there any particular effect of a spinal cord injury on protein metabolism?*

MAJOR SPRINZ Yes. After any type of injury, but particularly after a spinal cord shock or injury, a peculiar phenomenon occurs in well nourished individuals such as these soldiers were at the time of injury. It consists of a precipitous breakdown of a large amount of body protein and excretion of the nitrogenous end products in the urine. It leads to a serious depletion of the body and accounts for the very rapid weight loss following the injury. It is spoken of as

"toxic loss" of protein. It varies in magnitude, depending upon the severity of the insult. It is self-limited. It is independent of fever and the basal metabolic rate. The exact mechanism of the toxic loss of protein is still unknown.

COLONEL DUNCAN *This sudden deprivation of body protein, in contrast with the slowly developing avitaminosis, deserves emphasis. Maybe at this time Major Kleinman will tell us of the regimen for treatment of malnutrition at Halloran General Hospital.*

MAJOR KLEINMAN There are two fundamental principles in our treatment. One consists of efforts directed toward the removal or amelioration of the factors causing the malnutrition. The second is the provision of an adequate food intake. Specifically, the intensive program of activity, education and treatment gives these patients a more hopeful outlook for the future and helps considerably in lifting the state of mental depression. They come to realize that much can and is being done for them and are cheered by visible and tangible evidence of progress in themselves and others about them. The grouping of patients in several different wards, according to the degree of progress which they have attained, has proved to be a great morale builder, as patients find themselves being graduated from a ward of lesser activity to a ward of greater activity. With respect to the second principle, that is, the provision of an adequate food intake, the problem is complicated by several factors. First, *anorexia* is a most prominent feature. Most patients in this group exhibit an aversion to protein foods, in general, and to meat, in particular, thus creating difficulties in providing an adequate protein intake. Most patients express a desire for green and leafy vegetables and salads, but while the desire for these foods is commendable and desirable, the caloric and protein values are, of course, low. To help overcome these difficulties, patients are permitted a choice of one of two main dishes at each meal. The nurses, dietitians, and Red Cross volunteer dietitian's aides cooperate in serving and persuading the patients to consume all the food. A special effort is made to see that the food is served hot, and served attractively. The routine diet of the paraplegia section contains, as served, at least 3000 calories, including 125 gm of protein. Furthermore, each patient is required to drink an extra quart of milk daily in addition to any milk included in his regular diet. The chief purpose of this extra quart of milk is to provide an additional 35 gm of protein to make a daily total of 160 gm. Every effort is made to see that the patients actually consume all of the prescribed diet. Sandwiches served at bedtime are a regular part of the diet, and also help to make up for any food which the patients have refused during the day.

COLONEL DUNCAN *Major Sprinz, have you any comment to make on this problem?*

MAJOR SPRINZ I am in complete agreement with Major Kleinman, and just wish to emphasize that there is a limit to the amount of ordinary foods which a very sick patient can actually chew. We found that this limit is approximately 120 gm of protein. Most of the patients are able to eat only 80 to 90 gm of protein of regular foods though an occasional patient is capable of consuming 145 gm. As these patients are in such a great need of protein, a therapy of over-feeding is indicated. The means available to achieve hyperalimentation, particularly protein hyperalimentation, are the protein hydrolysates and amino-acids for intravenous and subcutaneous use, the protein hydrolysates for oral use, and the processed proteins in the form of milk powder, edible casein, and lactalbumin.

COLONEL DUNCAN *What method did you use in getting high protein diet into these patients?*

MAJOR KLEINMAN In the first place, that extra quart of milk, which I mentioned before, served as an extra protein ration to bring up the total protein intake. In the more severely depleted patients, instead of the extra quart of milk, a quart or more of one of the milk formulas, devised by us with the assistance of Captain Erma G. Lord, H.D., was given. This increased the total protein and caloric values considerably. A patient receiving a quart of formula II-A (see at end of discussion), for example, consumes approximately 220 gm of protein, that is, 125 gm. in the diet and 95 gm. in the formula. The formulas are given with, or shortly after, the regular meal, to avoid a diminution in appetite for the next meal.

COLONEL DUNCAN *What have been the results in feeding patients with protein hydrolysates?*

MAJOR SPRINZ We have had experience both with the parenteral administration of protein hydrolysates as well as oral administration. We, so far, have used only 2 parenteral solutions, Amigen and Baxter Protein Solution. Both solutions are safe in routine use. In our limited experience, we prefer Baxter Solution, as we had not a single case of a pyrogenic or depressor type reaction, while with Amigen we had several, including a "near fatal" one. Protein solutions are ideal culture media and any organism introduced into the bottle at the start of the infusion will have sufficiently multiplied at the end of two hours to give a reaction. Protein solutions are slightly acid and slightly hypertonic. With care, any thrombosis of the vein may be avoided even if the protein solution is fortified by 5 to 10 per cent glucose by adding 50 per cent glucose to the bottle of protein solution. The disadvantage of parenteral administration of protein

is that we are dealing with chronically ill and chronically depleted patients who require a regime of over-feeding over a prolonged period of time. For this reason, the oral feeding is the appropriate route of administration. Protein hydrolysates are highly nutritious protein foods, but are lacking in some of the essential nutrients as minerals, vitamins, and fatty acids. They have a very objectionable taste which is very difficult to disguise, while the milk formulas are palatable, well tolerated by most of the patients, and are complete foods, lacking chiefly Vitamin C.

COLONEL DUNCAN *In brief, what have been the results from the regimen just outlined?*

MAJOR KLEINMAN Under this regimen, most patients regained weight, accompanied by a marked improvement in their general condition. Under the regimen of hyperalimentation most patients regained their desire for food. In most instances, in which very high protein intakes were necessary at the beginning, as the nutritional state improved, there was a decreased desire for the extra protein. Wound healing was accelerated and this was particularly noticeable in the healing of those decubitus ulcers which were not extensive enough to require surgery. This regimen of high caloric and high protein feeding increased the patient's resistance to infection. In many instances there was noted a definite relationship between the degree of nutritional improvement and a decrease in the incidence of infection.

SPECIAL FORMULAS

These formulas consist essentially of milk fortified with powdered milk and egg proteins. When mixed in the proportions outlined below, they are very palatable and digestible. The palatability is increased for each patient by sweetening and flavoring to taste. Thorough beating of the eggs and careful mixing of the ingredients are important factors in producing a smooth, stable, and tasty mixture.

A very few patients developed diarrhea when they were started on formula III-A or III-B. This was probably caused by the high fat content of these formulas. The diarrhea promptly subsided when formula I-A or I-B was substituted, and did not recur when after a few days the formula was changed to II-A or II-B, and then to III-A or III-B. Accordingly, our policy is to begin with the weaker mixtures and change gradually to the richer mixtures. It will be noted from the analyses of the formulas that they are nearly perfect foods in themselves, containing nearly all of the essential nutrients.

In most cases one quart of formula plus regular diet will be sufficient. Where it is desired to give still more protein, a high protein diet may be prescribed with or without any increase of quantity of formula.

MILK FORMULAS I

I A

Food	Cm	C	P	F	CaL	Ca	P	Na	Cl
Powdered skimmed milk $1\frac{1}{4}$ cups	175	91	61	2	625	2 065	1 510	740	1 400
Skimmed milk 1 pint	500	25	17 5	1	180	610	480	255	550
Egg whites 6	150		18		0	023	021	255	231
Sugar, $\frac{1}{2}$ 1 tablespoon	15	15			60				
Total		131	96 5	3	915	2 698	2 011	1 250	2 183

I B

Powdered skimmed milk $\frac{3}{4}$ cup	100	52	35	1	345	1 180	840	400	800
Skimmed milk 1 pint	500	25	17 5	1	180	610	480	255	550
Egg whites, 6	150		18		70	024	021	255	231
Sugar, $\frac{1}{2}$ 1 tablespoon	15	15			60				
Total		92	70 5	2	665	1 813	1 381	910	1 583

II A

Dryco $\frac{1}{2}$ $1\frac{1}{4}$ cups	185	85	59	22	775	1 850	1 498	740	1 480
Skimmed milk, 1 pint	500	25	17 5	1	180	610	480	255	550
Egg whites, 6	150		18		70	023	021	255	233
Sugar, $\frac{1}{2}$ 1 tablespoon	15	15			60				
Total		125	94 5	23	1085	2 483	1 999	1 250	2 263

II B

Dryco $\frac{1}{2}$ $\frac{3}{4}$ cup	100	45	32	12	420	1 000	810	400	800
Skimmed milk, 1 pint	500	25	17 5	1	180	610	480	255	550
Egg whites, 5 plus one yolk	175		20 5	6	135	013	110	269	247
Sugar, $\frac{1}{2}$ 1 tablespoon	15	15			60				
Total		86	70	19	795	1 653	1 400	924	1 597

III A

Dryco, $\frac{1}{2}$ 1 cup	150	60	48	18	630	1 500	1 215	600	1 200
Milk 1 pint	500	25	17 5	20	350	600	465	255	530
Eggs, 4	200		24	24	310	136	448	280	212
Vanilla ice cream, $\frac{1}{4}$ pint	125	28	5 5	13	270	188	150		
Sugar, $\frac{1}{2}$ 1 tablespoon	15	15			60				
Total		137	95	77	1620	2 424	2 278	1 135	1 942

III B

Dryco, $\frac{1}{2}$ $\frac{3}{4}$ cup	100	46	32	12	420	1 000	810	400	800
Milk 1 pint	500	25	17 5	20	350	600	465	255	530
Eggs 3	150		18	18	235	102	336	210	159
Vanilla ice cream $\frac{1}{4}$ pint	125	28	5 5	15	270	188	150		
Sugar, $\frac{1}{2}$ 1 tablespoon	15	15			60				
Total		114	73	65	1335	1 890	1 761	865	1 489

Figures represent amounts per quart of formula.

$\frac{1}{2}$ Flawing added to each formula.

$\frac{1}{2}$ Amount of sugar varied to taste for individual patient.

$\frac{1}{2}$ Powdered skimmed milk may be used instead of Dryco. In such formulas, the f t content will be lower but can be compensated for by the addition of cream.

Ordinarily, the formula need not be changed beyond II-A. However, where the formula is the sole or the chief source of nourishment, then a further step up to III-A should be made. Patients are to get 2 quarts or more a day.

If diarrhea develops and it is believed to be due to the formula, change back to I-B and increase gradually to I-A and then II-A.

If digestion is fairly good, one may start with II-A or II-B instead of I-B. The total daily caloric intake should be at least 4000 calories in the very poorly nourished.

In all cases in which both ordinary food and formula are prescribed, the latter should be given with or not too long after meals, in order not to decrease patient's appetite for the next meal.

We are beginning to realize the importance of the intestinal flora of the human gut in the biosynthesis of amino acids, as well as some vitamins, in particular riboflavin, nicotinic acid and vitamin K. Some investigators¹ claim that a considerable proportion of these vitamin requirements of the human can be met in this manner. However, the faculty to synthesize vitamins varies greatly from person to person. This may explain the divergent views held by different authorities on the human requirements, particularly of the B vitamins.

In recent years we have come to appreciate more the biological interdependence of the various nutrients. Vitamin B is necessary for the metabolism of carbohydrates. Proteins are not well utilized without carbohydrates. Water and electrolyte balance are linked to protein metabolism. Protein depletion of the tissues causes an increase in interstitial fluids.

IMPORTANT ROLE OF PROTEIN IN THE BIOLOGICAL PROCESSES

The emphasis on the importance of various nutrients now has been shifted from vitamins to proteins. Proteins again have assumed the principal role for which they got their name (Greek, "first") and Rubner's statement, made a couple of decades ago, that "protein contains the magic of life," is utterly modern. Accordingly, this presentation will concentrate on the single, most important advance in our knowledge of nutrition, the subject of protein deficiency states.

Tissue Protein—Protein is an essential constituent of every living cell, the nucleus as well as the cytoplasm. Specialized proteins are the substrates of hormones, enzymes and immune bodies. Obviously, then, an adequate amount of protein is essential to life. There is an absolute minimum below which the living tissue protein content of a cell cannot sink without death. Under most circumstances, cells contain considerably more protein than the absolute minimum. Some of these are in an apparently labile form and readily available to the body if the need should arise. This portion of cellular protein has been called "deposit protein" by Rubner. Boothby has measured the "deposit protein" in the human. In a well nourished, average sized man it amounts to about 2000 gm. This is actually a very small reserve because, as we shall see later, great losses of protein do occur, particularly during acute illnesses and severe injuries.²

Plasma Proteins—In addition to tissue protein, there is also the "circulating protein" of the plasma. A dynamic equilibrium exists between cellular proteins and circulating plasma proteins. Plasma protein is made up of three constituents, globulin, fibrinogen and albumin. Each of the fractions of plasma proteins has its characteristic physical and physiological action. The globulin fraction has been subdivided, by means of electrophoresis, into alpha, beta and gamma globulins. Serum albumin and fibrinogen are predominantly formed in the liver while the globulin is formed by cells of the lymph nodes. Serum albumin

has the smallest molecular weight of all the plasma proteins. It is mainly responsible for the maintenance of the oncotic pressure of the blood, it is the protein which is lost in the urine in the nephrotic syndrome, it is the main constituent of the protein lost in exudates, and it is the protein usually affected in hypoproteinemia.

Results of Depletion of Tissue Proteins on Serum Proteins—Since a "dynamic equilibrium" exists between tissues and the serum proteins, a lowering of the serum albumin level occurs only after a serious depletion of the protein stores of the body. The magnitude of this loss has been determined by Elman, who found that a reduction of 1 gm. in the total circulating serum albumin entails the destruction of 30 gm. of body protein. Applying Elman's findings, let us assume that a man weighing 70 kg. has a total circulating plasma volume of 3000 cc., and that his plasma contains 4 gm. per 100 cc. of albumin. He therefore has a total of 120 gm. of albumin in the circulation. Then he becomes nephrotic and loses so much albumin into the urine that his serum albumin is lowered from 4 to 3 gm. per 100 cc. If the total plasma volume has remained the same, this entails a reduction from 120 to 90 gm. of his total circulating plasma albumin. This 30 gm. loss of serum albumin is the resultant of the destruction of 900 gm. of body protein. Nine hundred grams of body protein expressed as "flesh" is equivalent to approximately 4500 gm. of 'lean meat'. To summarize in a person of given weight and plasma volume, the reduction of 1 gm. per 100 cc. of serum albumin in the plasma corresponds to the loss of 10 pounds (4500 gm.) of flesh.

The changes of the serum globulin fractions follow a more complicated pattern. Cannon pointed out that our customary reliance in the total globulin determination may be inadequate and that in certain conditions a concentration of alpha and beta globulins may mask a serious depletion in the immune body carrying gamma globulins. It is generally accepted that depletion of body protein is reflected in the level of plasma protein particularly in the albumin fraction. However the level of plasma proteins is not an absolute indication of the state of the body proteins. In the presence of a normal or even high normal plasma proteins level there may be marked depletion of tissue proteins and only in the presence of low or diminishing plasma proteins may an inference be drawn as to the state of the tissue proteins. If only the amount of plasma proteins in grams per 100 cc. is determined, two additional factors have to be taken into consideration: (1) reduction in circulating proteins may be masked by a diminution of plasma volume; (2) hypoalbuminemia, a characteristic finding in protein deficiency, may be masked by an increase of serum globulins. This occurrence has been observed particularly in chronic infections.

In our own experience with a group of seriously depleted soldiers with chronic infections who lost from one-third to one-half of their original body weight following injury we observed that despite a

profound loss of tissue proteins, there was no hypoproteinemia and no abnormality in the albumin-globulin ratio. As a matter of fact, in a series of about fifty cases, the total circulating plasma proteins were, in general, normal or slightly higher than would have been expected for the particular weight of the patient. Charles C. Lund has made a somewhat similar observation in thermal burn cases. He found that with a slow development of a slight, long-time protein deficit, the plasma protein remained nearly normal, until there was a great decrease in the body stores, and at times he found patients with only slight lowering of the plasma protein value who were, in fact, greatly depleted. These observations are contrary to the generally held concept that severe depletion of tissue proteins results in hypoproteinemia.

The Amino Acids—Protein of either animal or plant origin contains 16 per cent nitrogen. It is customary to express protein as nitrogen using a factor of 6.25 for reconversion of nitrogen into protein. Proteins are not absorbed into the body as such but in the form of their constituent parts, the amino acids. The breakdown of proteins into amino acids and the absorption of the amino acids into the portal circulation takes place in the small intestine. There are twenty-two amino acids, the combinations of which form the various protein molecules. Ten of the amino acids are at present considered essential, because we believe they cannot be manufactured in the body, and because they have specific, essential functions in the body metabolism. They must be supplied in the diet. Proteins differ in their value to the body, depending on the digestibility of the protein on one hand, and on the suitability of the component amino acids as building stones of body flesh on the other hand. The digestibility of proteins determines the amount of amino acids absorbed into the circulation. The digestibility of all proteins of animal origin is uniformly very high. This is contrary to commonly held beliefs that appreciable differences exist, for instance, between lean pork and the meat from the breast of a chicken, or between "light" and "dark" meats. Proteins of plant origin are less digestible than animal proteins. The rate of absorption of amino acids per se is as high as that of alcohol or glucose. It is well to remember this point in the therapy of protein deficiency states. It has been our experience that processed proteins such as skimmed milk powder, powdered casein, or lactalbumin powder are just as effectively utilized as amino acid mixtures ("protein hydrolysates"). Exceptions are conditions which produce hypermotility, such as high intestinal fistula and regional ileitis, and those which are characterized by hypoenzymatic secretions, such as pancreatic fibrosis.

Superior and Inferior Proteins—The character of the proteins is very important to nutrition. A protein of high "biological" value is one which is highly utilizable, and which closely resembles body protein in its composition. An inferior protein is one which is lacking qualitatively and quantitatively in one or more of the amino acids which

are essential to the body metabolism. Such an inferior protein is poorly utilized, and commensurate with its deficiency, there is wastage of the dissociated nitrogenous end products. The wastage derives from two sources: (a) from the amino acids of the biological inferior protein which, instead of entering into the tissue protein metabolism, are immediately broken down and excreted, and (b) from the body tissues which, in the meantime, have to be broken down in order to furnish essential amino acids for the protein metabolism. Meat, dairy products, fowl and fish are our main sources of protein of high biological value. Many proteins of plant origin are lacking in essential amino acids, but are valuable as supplements.

An average, well balanced, mixed diet taken by a healthy individual contains all essential nutrients, including the amino acids necessary for the maintenance of optimal nutrition. It is only when the protein food intake becomes restricted that it becomes very important to assure the intake of proteins of high biological value. One point may be mentioned in this connection. In the human, protein deficiency rarely, if ever exists by itself. Protein foods of animal origin are at the same time important sources of vitamins, particularly B complex, and of minerals (calcium, others). Consequently, when inadequate food intake is the cause of the protein deficiency, other essential nutrients will also be inadequately supplied. In addition any condition which interferes with absorption will not only affect protein but these other substances as well. In cases where the protein deficiency is due to excessive metabolic destruction as in acute illnesses and injuries, other essential substances are also affected, for example, vitamin C, as demonstrated in surgical wound disruptions.

Nitrogen Balance—In a normal individual on an average diet, there is a perfect equilibrium between the protein nitrogen intake and output. On a dietary intake of 70 gm of protein a day for a man weighing 70 kg (1 gm of protein per kilogram of body weight) the nitrogen loss amounts to about 10 gm a day. Under ordinary circumstances, 90 per cent of the end products of nitrogen metabolism are excreted in the urine, and about 10 per cent in the feces. The loss from other sources—hair, nails, sweat—is negligible. In case this "nitrogen equilibrium" is disturbed by, for instance, a disease process, and more tissue protein is broken down and lost than is assimilated, a negative 'nitrogen balance' ensues. In the process of recovery from the illness, the reverse will be true, and more protein nitrogen will be retained than is excreted. A positive 'nitrogen balance' will result until the deficit is made up. When the cells of the body have obtained their optimal protein content, they lose their power to attach additional protein, and nitrogen equilibrium is again established.

In nitrogen equilibrium, the amino acids which are not required for the restoration of tissue proteins, for the building of hemoglobin or plasma proteins, for the manufacture of hormones or of intestinal

secretions, are broken up. They are deaminized. The nitrogenous end products are excreted in the urine, and the rest transformed into carbohydrates, and used as such. One hundred grams of amino acids yield 58 gm of carbohydrates. Once nitrogen balance is established, additional feeding of protein leads to increased metabolism of protein and establishment of nitrogen equilibrium at higher levels of intake and output. The body has a very limited ability to store protein nitrogen in reserve, as was mentioned previously.

Factors Affecting the Metabolism of Protein—There is a constant turnover of protein in the body, a certain amount of wear and tear which has to be repaired, and the demands of the protein metabolism will be met, as long as there is life, from either the protein stores of the body or from the dietary intake. The amount of protein metabolized over a given period depends on a number of variables, some of which we have already discussed: (1) the level of protein stores of the body, (2) special demands made during certain physiological states, such as growth and lactation, or special demands made during periods of illness, injury or convalescence, (3) the energy or caloric requirements of the body.

It is a general law of metabolism that the caloric or energy requirements of the body must be fulfilled. Proteins, fats and carbohydrates are the three essential nutrients which furnish energy, at the rate of 4, 9 and 4 calories per gram, respectively. As far as the caloric needs of the body are concerned, the three nutrients are interchangeable, a fact which has been referred to as the "protein-sparing" action of fat and carbohydrates. However, there is a difference between fats and carbohydrates, in that carbohydrates have a specific "protein-sparing" action, which is independent of the energy metabolism. Fat, when given as the sole source of food, has none of the specific "protein-sparing" action. As a matter of fact, it is difficult to establish nitrogen and energy equilibrium without carbohydrates.

In health, when an average mixed diet is consumed, all these factors are well taken care of. However, when malnutrition is actually present or threatening, the relations between the protein needs and the energy needs of metabolism assume great importance. In the beginning of a starvation period, when an individual is still in good nutritional state, the amount of protein metabolized is in a constant ratio to the total metabolism. Under such conditions, it is estimated that approximately 13 per cent of the caloric requirements of the individual are met by burning up body protein, and that the rest of the calories are derived mainly from fat. Protein catabolism will be lowered during the course of uncomplicated starvation, such as, for instance, during a rigid and prolonged reducing diet, until it reaches a "starvation minimum." Starvation is said to lower the basal metabolic requirements. However, this is not true in every case. In our group of markedly depleted soldiers, some of whom characteristically manifested chronic

infections without fever, elevated basal metabolic rates up to 25 per cent, were recorded

The body uses approximately 2000 calories daily. If this energy is not furnished in the diet, the body burns up its own reserve. In this connection, it is well to remember that 100 gm. of fat yields 900 calories, and 100 gm. of "flesh," approximately 80 calories. About eleven times more "flesh" by weight than fat has to be metabolized to yield the same amount of calories. Protein catabolism will greatly increase as soon as the fat stores of the body are exhausted. The older nutritionists were well familiar with this phenomenon and spoke of it as the "terminal rise" of nitrogen excretion, because the experimental animal or human would die shortly after its appearance. During starvation, the length of life depends upon the amount of fat present. Storage fat has no vital biological function and can be sacrificed to the caloric needs of the individual without harm. Depletion of protein, however, has an immediate and serious effect on the body because protein partakes in every biological process.

Many decades ago, Voit demonstrated that one may have nitrogen equilibrium without having energy equilibrium. That is to say, the body may still lose weight by burning up fat when sufficient protein nitrogen is supplied to attain nitrogen equilibrium. This knowledge has long been applied in the treatment of obesity, by giving a protein-rich, fat-poor, low caloric diet. This principle has not been sufficiently utilized in prescribing diets in protein deficiency states, and has recently been reemphasized by Elman,² who considers the replacement of protein loss in acute starvation of primary importance, while he disregards caloric intake. Voit likewise demonstrated that, in dogs nitrogen equilibrium was reached only after supplying three and one-half times the amount of protein metabolized during the period of acute starvation. We have made similar observations in our patients with infected battle wounds. We have no explanation for this phenomenon, but it has an important bearing on the therapy, since enormous "overfeeding" is necessary.

Of all the factors which influence the amount of protein metabolized, none is as outstanding as the *increased demand due to illness or injury*. The recognition of this fact represents one of the greatest of recent advances in the science of nutrition. While the daily nitrogen loss during a starvation experiment of a healthy volunteer never amounts to more than 5, maybe 10 gm. of nitrogen, the loss during disease reaches several multiples of that, regardless of whether we are dealing with a pneumonia, empyema or typhoid fever, or a burn, war injury, fracture of the long bone, or any type of surgery be it an appendectomy or an abdominoperineal resection. The magnitude and the duration of the protein loss differ with the severity of the condition. It is most marked in well nourished individuals, it is self limiting, and it is independent of the caloric requirements of the body,

and of fever. The exact mechanism of this phenomenon is still debated. It is spoken of as the "toxic destruction of protein." There is no general agreement as to whether the massive loss of protein during the acute phase of the "toxic destruction" can be compensated for by protein replacement therapy. Several investigators feel that protein given during this phase is "short circuited," i.e., is immediately broken down and is excreted and has no body protein-sparing effects, but this is not generally accepted. The difficulty of feeding 200 to 300 gm of protein per day to sick patients is real, yet this amount is necessary to compensate for the destruction of protein in certain severe acute cases. On the other hand, there is no question that the loss of protein due to "toxic destruction" can be compensated for by appropriate therapy. There is also definite proof that the postoperative loss of protein can be overcome after appendectomy, herniotomy, cholecystectomy, and gastrointestinal resection.

Another source of nitrogen loss to the body which only recently has received attention is pus and exudation from burn surfaces and wounds. The magnitude of this loss of nitrogen varies. In large empyemas or extensive burns, it may reach 40 gm of protein (6.4gN) a day. We determined the loss in cases of suppurating compound, comminuted fractures of the femur and of the pelvis, and found it to approximate 10 to 15 gm (1.5-2.0gN) of protein per day.

DIAGNOSIS OF PROTEIN DEFICIENCY

The detection of protein deficiency is not always easy. One has to rely on a carefully taken nutritional history, and a physical examination which includes a simple physical fitness test (exercise tolerance test). Strength and endurance curves which are measured by a physical fitness test, or by an ergograph,* are important and objective indications of the state of protein nutrition in the absence of complicating factors. In our experience, determination of strength is more dependable than reliance on the weight curve of the patient. The weight is an important but not an entirely reliable criterion, due to the possibility of large fluid shifts, which may mask the loss or gain of flesh. A few simple laboratory procedures are valuable aids, such as the determination of hemoglobin, plasma protein, albumin and globulin ratio. In all of our cases of malnutrition, we noted an anemia which was persistent and rather refractory to therapy. A low plasma protein, and a low albumin-globulin ratio are strong indications of an existing state of protein deficiency.

The clinical recognition of the importance of protein deficiencies has long been delayed due to the fact that practical quantitative methods were not available to determine such deficiencies. Only in

* The ergograph we are using has been designed by Dr. Co Tui and is manufactured by the Clay-Adams Company in New York. It is a modification of the one previously described by him.⁴

recent years study of nitrogen balance has been used to investigate a variety of diseased conditions, particularly in connection with studies on rehabilitation and convalescence from surgical and medical diseases. Complete nutrition studies now include "nitrogen balance study," which gives information on the metabolism of whole protein, the "amino acid balance study," which follows the fate of single amino acids, blood volume determinations,* total circulating protein determinations,† determinations of the "available fluid space,"‡ which gives some indication of the amount of interstitial fluid in the body, and various tests of physical fitness, notably the ergograph. A full field of investigation has been opened, and much is still to be done, but the results so far obtained by the investigators permit drawing of the following conclusions. Protein deficiencies cause a variety of symptoms, the combination of which will vary in the individual case. There is a *mental depression* which may progress to apathy, confusion, and incontinence of urine and feces. There is *lack of appetite*, and *weakness and lassitude*. Obviously, these symptoms are very indefinite and may be caused by other conditions. In many instances they were taken by the attending physicians as the inevitable consequence of postoperative state. However, nothing is as striking as to see these symptoms disappear in a few days of a regimen of "hyperalimentation," which will be described in detail later.

Protein deficiency is commonly accompanied by a *loss of weight*. This loss of weight may be masked by a considerable increase of interstitial fluid. Many liters of excess interstitial fluid may be "hidden" and may never become apparent. *Nutritional edema* is one of the last phenomena of advanced protein deficiency, and may be absent, even in fatal cases. In our own observations, nutritional edema has been very uncommon, both in the group of returnees from German and Japanese prison camps who suffered from the effects of starvation, as well as in the group of soldiers in whom serious depletion was the consequence of war wounds. Conversely, loss of weight may be one of the first signs of improvement. As a positive nitrogen balance is established and the nitrogen is retained in the body, water is given up. When this happens, the turgor of the skin greatly improves.

EFFECTS OF PROTEIN DEFICIENCY ON WOUND HEALING RESPONSE TO INFECTION ETC

The effect of protein deficiency on wound healing is well established. Bed sores, disruption of wounds, localized edema around suture lines, particularly in the gastrointestinal tract, are invariably connected

Plasma volume is determined by the dye method using the F 1824 and a Nickerson Decade Photometer.⁶

† The total circulating proteins are calculated on the basis of plasma volume and total protein in grams per 100 cc. of plasma.

‡ The "available fluid space" is determined by the sodium thiocyanate method.⁶

with protein depletion of the body, and the effect of protein hyper-alimentation is truly remarkable in these conditions. Even the largest bed sores we have seen amongst our patients with spinal cord injuries heal rapidly. Without any additional specific chemotherapy, the granulation tissue changes in character, from sloughing to healthy, and epithelization begins. These observations suggest that the pressure ulcerations of paraplegics are in effect caused by massive protein loss, and that they can be favorably influenced by protein replacement therapy.⁷ The same favorable effects have been observed on the course of peptic ulcers. Co Tui and his associates demonstrated convincingly that peptic ulcer patients, both those who came to operation and those who were treated medically, did better if they were fed with an abundance of highly utilizable proteins. This represents an advance over the Sippy diet regimen.

During this war I performed a series of autopsies on patients who suffered from severe malnutrition. There was one common finding: an edema of the walls of the stomach, and particularly of the walls of the small intestine. It is possible that a connection exists between this edema and the anorexia commonly observed in malnutrition. Clinically, as soon as the protein deficit is overcome this edema disappears, and the patient develops a ravenous appetite.

An important aspect of the protein deficiency states is the effect on the response of the patient to infection. Cannon has emphasized the fact that both the production of humoral antibodies (the gamma globulin fraction of the plasma), as well as the production of phagocytes are inhibited under such conditions. This probably accounts for the susceptibility of malnourished patients to intercurrent infection and for the fulminating course which these infections take. Not only are the depleted patients an easy prey to respiratory, gastrointestinal and skin infections, but, in the event that surgery becomes necessary, the possibility of the spreading infection is greatly enhanced. The post-operative progressive bacterial synergistic gangrene, which was first described by Meleney, only occurs in depleted patients. This condition follows drainage of chronic suppurating chest and abdominal infections. The progressive gangrene of skin and subcutaneous tissues around the incision is caused by the symbiotic action of a micro-aerophilic, nonhemolytic streptococcus and a hemolytic staphylococcus. Lack of immune response in these depleted cases favors the spread of the gangrene. Since the advent of effective chemotherapeutic agents which are capable of controlling formerly fatal infections, the protein deficiency syndrome incident to these infections looms increasingly more important. Armstrong⁸ recently illustrated this point. Of the two cases cited in his report one was a young man with pneumococcal pneumonia involving four lobes and the other an elderly male with staphylococcal pneumonia which complicated prostatic surgery. In both instances the infection was promptly controlled by penicillin.

However, a serious protein deficiency syndrome developed and the convalescence was stormy and prolonged. Armstrong feels that the active protein replacement therapy he employed was instrumental in saving the lives of the two patients. This confirms the experience at this hospital in surgical infections.⁹ The replacement of protein loss is one of the most important adjuvants in shortening the period of convalescence and rehabilitation.

PROTEIN DEFICIENCY AS COMPLICATION IN VARIOUS MEDICAL AND SURGICAL CONDITIONS

Metabolic Disturbances—In *thyrotoxicosis* the caloric requirements of the body are greatly increased, due to the characteristic rise in the metabolic rate. If this need is not met, extreme weight losses do occur. Such losses not only affect the functionally unimportant fat stores, but also the muscle and organ proteins. A high protein, high caloric diet is therefore indicated in conjunction with specific measures such as iodine or thiouracil medication, and surgical intervention. Similarly, increased catabolic processes are the source of marked protein loss in uncontrolled or poorly controlled *diabetes*. The excessive nitrogen and sugar excretion in the urine is the result of increased glycogenesis (breakdown of protein and transformation of part of the radical into sugar). Insulin in proper dosage will correct this loss. However, additional protein must be supplied in order to correct any existing deficiencies.

Psychoneurotic and Neurologic States—Deficiency states are primarily dietary in origin. The dietary intake may be restricted for economical reasons, due to habits and aversions, due to certain preconceived ideas, e.g., that meat is harmful, due to religious scruples, due to allergy against milk and egg products. For unknown reasons, protein needs appear to be higher in certain persons who develop signs of a protein deficiency state under an apparent adequate intake. A high protein diet brings an immediate response in such cases. Poor appetite or nausea incident to acute febrile or chronic diseases, emotional stress, tropical climate, to name just a few conditions are probably the most common causes of a protein deficiency state. Malnutrition may develop in psychoneurotic conditions such as *anorexia nervosa*, frank psychoses characterized by voluntary restriction of intake, or in *neurological conditions* as illustrated by the following case.

CASE I—A 24 year old American soldier developed a severe sore throat with cervical lymphadenitis. A few days later on November 18, 1944 the patient woke up with pain in the lower back, which lasted for about two hours and following which he noticed weakness in the legs. The next day he could only wiggle the toes of his right leg. The paralysis rapidly ascended and his arms were affected two days later. Slight motion of the arms remained; sensation was diminished. Gradually sensation returned to the arms and was restored by February 1945. Three months later Sphincter control was lost since the onset, and a cystostomy

was performed on December 29, 1944 (Previously, the patient had been catheterized) The temperature throughout was normal

At the time of admission to Halloran General Hospital on May 29, 1945, there was limited return of function in the patient's upper extremities However, the status of the lower limbs, and the sphincter paralysis, remained unchanged His usual weight had been 163 pounds At the time of arrival it was 113 pounds He was 5 feet 11 inches tall and was obviously very malnourished The skin was dry and scaly There were large decubital ulcers over the sacrum, both femoral trochanters and both heels A suprapubic cystostomy was present The muscular system was atrophic, the legs more so than the arms There was some diminution in accuracy of finger movements The abdominal reflexes were absent There was very little voluntary movement in the lower extremities, none below the knees The patient exhibited involuntary mass reflexes and adduction response in the legs, when stimulated The muscles were spastic and apparently atrophic Deep reflexes and pathological reflexes were absent The loss of pain and temperature sensation had assumed a fairly good segmental distribution, sacral segments on the left and sacral and lower lumbar segments on the right However, there was a definite suggestion of peripheral (distal) distribution as well, particularly in light touch Deep sensation was markedly impaired below the knees Bladder and rectal dysfunction have been already noted The diagnosis was residual myelitis of the lumbosacral segments, complicated by severe malnutrition and bed sores

The patient was entirely helpless He had neither interest in food nor the strength to feed himself adequately He continued to lose weight and strength, and two weeks following admission his weight was 110 pounds, a total loss of 53 pounds On June 15, 1945, he was placed on a high protein, high caloric diet, and a determined effort was made to feed him the prescribed diet His daily intake during the next ten days averaged 3823 calories and consisted of an average of 216 gm of protein (34.5 gm of nitrogen), 339 gm of carbohydrates and 198 gm of fat Approximately half of the protein consumed was derived from the diet, the other half was given as supplementary feedings which consisted of milk powder, milk, eggs, and ice cream In this ten day period the patient gained but 2 pounds However, while the total "available fluid" prior to "hyperalimentation" was 19 liters, following the feeding period it was 14.6 liters, a loss of total "available fluid" of 4.4 liters This would indicate that by far more flesh was rebuilt than suggested by the 2 pounds gain of weight

After two weeks of "hyperalimentation" the patient was able to sit up, for the first time since the onset of his illness The decubital ulcers diminished in size, and by the second of July the decubitus ulcer over the lumbosacral region had almost completely healed and that over the right femoral trochanteric area was smaller Consequently, the patient was continued under a regimen of "hyperalimentation" for an additional two weeks His nitrogen intake was maintained again at around 0.7 gm of nitrogen per kilogram of body weight His caloric intake was slightly above 3000 calories per day, approximately 60 calories per kilogram of body weight He received, during the second period, 238 gm of protein per day (38.2 gm of nitrogen) During this period his protein requirements were exclusively supplied by "Essenaminate."* He showed steady improvement There was a noticeable increase in strength He was able to move about in a wheel chair and he noticed return of flexor motion in his lower extremities and hip joints but as yet was unable to extend his lower extremities The involuntary mass reflexes disappeared The loss of sphincter control of bladder and rectum remained On July 15 the patient was transferred

The importance of this case lies in the fact that convalescence was accelerated through "hyperalimentation"

* A lactalbumin preparation processed by Frederick Stearns & Co

Chronic Diseases of Lung, Kidney and Liver—The principle of hyperalimentation is applicable equally to the treatment of deficiency states accompanying cancer, tuberculosis, Bright's disease, liver cirrhosis and so forth. It cannot be overemphasized that malnutrition exists coincident with a primary disease, that malnutrition is a serious complication, and that it is amenable to therapy. Even in Bright's disease, as long as there is no azotemia, a regimen of "hyperalimentation" can be instituted without any evidence of a deleterious effect. The following case may serve as an illustration.

CASE II—This soldier, 21 years of age, was wounded in action on April 9, 1945 by a hand grenade, several fragments of which tore into the right hip and posterior chest. He arrived in the United States on May 17, 1945. At that time he had a sustained temperature of 103° F and complained of severe pain in his right buttock and right hip area. There was a profuse purulent discharge from the right buttock and from a sinus in the right hip region. Several days later a large abscess beneath the right gluteus maximus was incised and drained. The patient arrived at Halloran General Hospital on June 8, 1945.

Upon admission the patient was very weak, nervous and apprehensive. He was 6 feet 1½ inches tall. His weight at the time of injury was 175 pounds, but on admission was 115 pounds, a loss of 60 pounds. There was a healed wound over the lower portion of the right chest posteriorly, the wound of entrance of a shell fragment (lodged in the liver). The patient had a white blood cell count of 10,200, hemoglobin 10.7 gm. Urinalyses showed a fixed specific gravity and the patient was unable to concentrate urine beyond a specific gravity of 1.010. Albumin and sugar determinations were repeatedly negative. There were occasional granular casts and leukocytes. Nonprotein nitrogen in the blood was 34 mg. and blood urea nitrogen was 23 mg. per 100 cc. The phenolsulfonephthalein excretion was 65 per cent in two hours, which is within normal limits. The urea clearance test showed a maximum clearance of 160 per cent and a standard clearance of 74 per cent, indicating that glomerular filtration was satisfactory and that the patient's difficulty was in tubular reabsorption, e.g., in concentration, hence the low specific gravity of the urine. On the basis of these findings we felt confident that the patient would be able to tolerate "hyperalimentation."

Following admission the patient ran a low grade fever and on June 15 the extensive sinus of the right gluteal region was saucerized. The patient was placed on a high protein, high carbohydrate, high vitamin diet, but no special efforts were made to check the amount of food actually consumed. The wound in the hip continued to drain, the temperature remained elevated, and the patient's appetite remained poor. For these reasons, on June 27 the patient was transferred to a special metabolic ward. Here, through the efforts of the dietitian, the hospital diet was made attractive and he consumed an average of 2920 calories a day. The entire food intake was supplied by natural foods only and included 112 gm. of protein (equal to 17.9 gm. of nitrogen), 260 gm. of carbohydrates and 159 gm. of fat. This provided 56 calories and 0.342 gm. of nitrogen per kilogram of body weight per day. The patient gained 5 pounds within a week. His general condition improved, his appetite became better and concomitantly the wound exudate lessened in amount. There was evidence of return of muscle strength. While on admission the patient was totally bedridden and hardly able to help himself. One week after "hyperalimentation" he was able to take a few steps with the aid of crutches. The wound in his right hip apparently was healing. The "available fluid" determination at the beginning of the study yielded a result of 20.2 liters. In the initial phase of the study the patient 6 pounds until his weight reached 121 pounds. By July 12 he had

pounds and his weight was 118¼ pounds. At that time his "available fluid" had dropped to 167 liters, a net loss of 35 liters. The amelioration of the protein deficiency brought about a shift of body fluids with loss of "hidden edema." On July 12 the caloric and protein intakes were increased. The bulk of the protein was supplied in the form of "Essenamint." The patient now received 0.69 gm of nitrogen, 37.1 gm of protein and an average of 70 calories per kilogram of body weight, or 3750 calories daily. Under this regime he continued to improve rapidly, and on July 16 he stated that he felt much stronger than before the nutritional program was instituted. In fact he was able to do "push-up" exercises, felt hunger pains between meals, and had food cravings. Within a month's time following institution of hyperalimentation therapy, he had again become alert and cheerful. He was able to get about good distances with crutches. His weight had reached 132 pounds. Kidney function tests remained normal.

This case illustrates several points. (1) It refutes the often made statement that proteins are dangerous in a chronic disease of the kidney, and emphasizes that each case has to be judged on its own merits. (2) The mere prescription of a diet is not enough. There must be complete coordination between attending physician, dietitian and patient with a close check on the actual food consumed, and immediate action must be taken to supplement the diet by other means, if food intake is inadequate.

As in this case, Stare, Thorn¹⁰ and Co Tui¹¹ likewise did not observe any kidney impairment from high protein feedings. Protein has proved to be an excellent diuretic in cases of hypoalbuminemia and edema incident to chronic kidney or liver disease, except in advanced stages. Even then, diuresis may be produced by parenteral protein administration, particularly in the form of concentrated human plasma. However, concentrated human plasma has the one disadvantage of containing a relatively large amount of salt which may counteract the diuretic action. The recently introduced serum albumin solution is salt-poor, and in it the albumin content of 500 cc of plasma (25 gm of albumin) is concentrated in 100 cc of diluent. It has proved in our experience a very effective diuretic under circumstances where no other measure would help. We observed a prolongation of life in two cases of advanced liver cirrhosis. One of the patients died from liver insufficiency, despite effective diuresis, while the other has been kept alive for several months by periodic infusion of serum albumin. It must be emphasized that in such advanced stages of cirrhosis serum albumin gives only temporary relief as it does not influence the production of serum albumin by the liver and the edema and ascites rapidly reoccur. Thorn has in addition reported considerable success in the treatment of edema in chronic kidney disease by use of serum albumin. He advocates the administration of 2 units of serum albumin (50 gm) diluted to 500 cc with 5 per cent glucose in distilled water at a rate of approximately 100 cc per hour. Pronounced hypertension and cardiac failure are contraindications to the use of serum albumin.

The recent widespread occurrence of *epidemic hepatitis* and homol-

ogenous serum jaundice has focused attention upon the role of proteins in hepatitis. In addition, we have become aware of the frequency of liver damage following anesthesia. While formerly a high carbohydrate diet was prescribed in the hope that glycogen would prevent liver damage, it is now felt that high protein intake is even more essential. In animal experiments the two sulfur groups containing amino acids, methionine and cystine, are particularly effective in ameliorating liver injury. The Second Service Command has been fully conscious of the problem and the following specific recommendations are in effect prescribing the dietary management of patients with hepatitis. The daily diet should contain 140 gm of protein, 400 gm or more of carbohydrates, and sufficient fat to provide a total caloric value of 35 calories per kilogram of the normal body weight. An allowance of 75 gm. of fat in form of dairy products and eggs is not only permissible but desirable. The dietitian should personally check the food trays during the "anorexia phase" of the disease, and give the doctor an account of the food not eaten. The difference between the actually consumed and the prescribed dietary intake is then given as an oral or parenteral supplement. The same beneficial effects of high protein feeding are accrued in liver damage resulting from anesthetic agents.

Diseases of the Gastrointestinal Tract—Diseases of the gastrointestinal tract comprise one of the most important groups which lead to protein deficiency states. The most commonly encountered are chronic peptic ulcer, chronic gastritis, regional ileitis, chronic pancreatitis, ulcerative colitis, and colitis due to or following bacillary or amebic dysentery as well as gastrointestinal malignancy. The factors by which these conditions lead to a deficiency state are loss of appetite and anorexia, restricted diets, vomiting, intestinal hypermotility with diarrhea, chronic melena, internal fistulous and draining sinuses. Edema of the bowel, the result of protein deficiency, in turn aggravates gastrointestinal dysfunction and a vicious cycle is set up. This observation is well known to surgeons, and the following case may briefly illustrate the point.

CASE III—A young German prisoner of war was shot in the abdomen, and sustained multiple perforations of small bowel, which were repaired. He made an uneventful recovery. Six weeks after the injury he suddenly developed an acute intestinal obstruction, which was relieved by intubation. When an attempt was made to remove the tube, the patient developed new symptoms of obstruction. Consequently, for about three weeks he was intermittently on Wangensteen suction and intravenous glucose and saline and short periods of oral feeding. His weight loss was 30 pounds. It was felt that he was in too poor shape to be explored and an attempt was made to prepare him for operation. He received 2000 cc. of a 5 per cent protein hydrolysate solution plus 2000 cc. of 10 per cent glucose and glucose and saline for four days. At the end of four days, small two-hourly feedings of a protein hydrolysate "Dextrin-maltose" mixture was given as supplement through the tube. At the end of one week the patient was able

to take a concentrated protein hydrolysate "Dextrin-maltose" mixture by mouth which supplied 0.6 gm of nitrogen per kilogram of body weight and 40 calories per kilogram of body weight, without any ill effect. In the second week, the patient developed a ravenous appetite, his recovery was considered complete, and surgical intervention was considered unnecessary.

Our explanation of the sequence of events in this case is that generalized or localized edema of the bowel aggravated an obstruction which was caused by postoperative adhesions. The edema was the result of a protein deficiency state which increased in severity under the therapy employed (suction and parenteral glucose and saline). As soon as the nitrogen balance was reverted from negative to positive the edema of the bowel disappeared and the obstruction was relieved.

Chronic gastrointestinal diseases present some of the most difficult problems from the point of view of nutrition. It is not always possible to treat such patients with oral feedings, and sometimes in these chronic cases the veins are in such poor condition that prolonged intravenous feeding is not feasible. For instance, in a case of *regional ileitis*, we were unable to achieve a positive nitrogen balance by oral feeding alone, even when proteins were given in processed form and the bulk of the food was reduced to a minimum. The hypermobility of the bowel was such that the patient lost more nitrogen than was offered him in the diet.

CASE IV—The patient, a 24 year old soldier, has had, for the past two years, typical regional ileitis, and two laparotomies for resection of ileum and antero-entero-anastomoses had been performed. His original weight was 148 pounds, his weight on admission 128 pounds. As a base line, the nitrogen balance of this patient was first studied while he received the regular hospital diet prescribed for him. During this one week period the patient did not lose any weight. However, our balance study indicated that he lost daily approximately 1 gm of nitrogen in urine and feces more than he received in his food. Then he was put on "Essenamint" and his daily caloric intake was increased from an average of 2600 calories or 44 calories per kilogram of body weight to 3500 calories or 59 calories per kilogram of body weight. His nitrogen intake was increased from 0.23 to 0.5 gm per kilogram per day. Although the patient gained 3 pounds in a ten day period, the average nitrogen loss during this period was 5.4 gm of nitrogen per day, as contrasted with the 1 gm loss on the regular diet.

This case illustrates the difficulty of supplying adequate nutrition in a case of chronic disease of the gastrointestinal tract. Only by constant attention to the dietary needs can serious depletion be avoided, such measures as repeated feeding of small quantities of highly nutritious food, supplemented by oral or parenteral administration of protein hydrolysates, amino acids, and protein concentrates, as well as liberal blood and plasma transfusions may have to be resorted to. One of the signs of the protein deficiency state is anemia. We have encountered in our cases of infected war wounds a protracted anemia which does not respond well to the administration of iron, liver extract, and high protein feeding and we can only confirm Lyons' observation that the

eradication of the infection appears to be a prerequisite to successful treatment. Similar observations have been made on anemia of gastric malignancy.¹² The exact mechanism of this phenomenon is not known. It is contrary to the commonly held concept that the formation of hemoglobin takes precedence over other body proteins. In general, hypochromic or nutritional anemia is primarily due to an iron deficiency, although experimental evidence would indicate, in addition, the desirability of an adequate protein intake of high biological value.

Surgery—The importance of protein deficiency states in surgery derives from the fact that protein is intimately linked to maintenance of blood volume, wound healing, tissue integrity, reestablishment of nervous reflex mechanism, production of antibodies, prevention or amelioration of liver injury incident to shock and anesthesia, and to convalescence. As was pointed out before, there is a "toxic" loss of protein nitrogen in every case of surgical trauma, wounds, injuries, operations, spinal shock, hemorrhage, burns and so on. Protein is lost through exudates.

In traumatic, hemorrhagic or burn shock the blood volume is reduced and plasma proteins are lost. It is by now well established that hypoproteinemia predisposes individuals to shock after any kind of injury. The problem of wound healing and the relation of protein deficiency to dehiscence of wounds has already been mentioned. Likewise discussed was the problem of bed sores, and of surface and gastrointestinal ulcers. Little known is the importance of a positive protein nitrogen balance in the reestablishment of a nervous reflex arc following *spinal cord injury*. The following case may serve as an illustration.

Case V—The patient, a 31 year old soldier, was wounded in action on January 5, 1945, when a bullet entered his right posterior thorax about 2 cm from the midline at about the level of the eighth thoracic vertebra, resulting in an immediate paraplegia with the sensory level at the umbilical plane. Fluid and air were present in his right chest, which were aspirated on several occasions. Approximately 5 days after injury he felt some sensory return to the legs; after two weeks he began to notice slight motor function in the left leg and in March he first experienced slight movement in the right leg. On admission to Halloran General Hospital, in March, 1945, the patient showed evidence of profound malnutrition. His normal weight had been 145 pounds. His weight on admission was 95 pounds. He was depressed, concerned over his condition, and so weak that he was unable to shave himself to pull himself up or even to feed himself a full meal. There were extensive decubital ulcers over both heels, left chest posteriorly and over the sacrum. A right pulmonic empyema was present. He was incontinent of urine and feces. There was a suprapubic cystotomy which was performed in February.

Neurological examination showed a partial paraplegia of both lower extremities, with slight function in all muscle groups on the left, and very slight function in the hamstrings and adductors of the right thigh. There were almost continuous mass reflexes involving both lower extremities which necessitated the wrapping of the legs in sheets to prevent the patient from falling out of bed. There was hypaesthesia in both lower extremities. The sensory level was at ap-

proximately D-g (level of umbilicus) The sense of position in the lower extremities was poor and vibratory sense was absent The legs were spastic and only slight patellar reflexes were elicited bilaterally The Achilles reflex was absent bilaterally, as was the Babinski sign

In early March a thoracotomy was performed to drain an empyema of the right chest, with release of about 1000 cc of pus At that time a bronchopleural fistula was noted Following thoracotomy the empyema cavity was irrigated daily with a saline penicillin solution The patient received multiple blood and plasma transfusions Despite better than average ward care and all generally employed supportive measures, the patient was slowly losing ground and it was decided to try him on a regimen of "hyperalimentation" On May 5 he was started on a ten day period of supplementary oral feeding with "Amigen"* and "Dextrin maltose," equivalent to 0.6 gm of nitrogen per kilogram of body weight and enough calories to furnish 40 calories per kilogram of body weight per day This formula was divided into eight doses and given at two hour intervals In addition to the supplementary feeding of "Amigen," the patient was encouraged to eat a full natural food diet If this formula is applied to an average male of 70 kilograms body weight, his supplementary food intake would amount to 42 gm of protein nitrogen or 262.5 gm of protein (42×6.25) and 2800 calories per day

The effect of this regimen was striking The patient gained 13 pounds during this ten day period, his spirits were buoyed up, and the decubital ulcers healed rapidly Subsequently, he developed a ravenous appetite During the next two weeks the patient lost 5 of his 13 pounds which he had gained during the first ten days However, by laboratory studies, he again showed the marked shift of interstitial fluids which was noted in other cases At the beginning of the study his total available fluid was 23 liters Following a month of "hyperalimentation" the available fluid dropped to 16.4 liters At the end of the month the patient was able to shave himself, to lift himself up, the motor function in both legs improved, the involuntary mass reflexes disappeared, the decubital ulcers of chest and heels completely healed, and the empyema cavity diminished greatly in size The bronchopleural fistula closed spontaneously The patient has shown progressive improvement since, he has regained control of his elimination, he is able to take care of himself and with the aid of special braces, even to walk

GENERAL PRINCIPLES OF TREATMENT OF THE PROTEIN DEFICIENCY STATES

If we apply what has been said about various aspects of malnutrition to the therapy of protein deficiency states, the following general principles evolve Prevention is better than cure, if unchecked, protein deficiency states may develop rapidly and may lead to dangerously large depletions After a severe state of malnutrition is established, it takes considerable effort and time to restore the patient to a normal state Protein must be given in sufficiently large amounts to compensate for the loss from various sources We found that in most cases very satisfactory results were obtained if from 0.4 to 0.6 gm of

* "Amigen" is an enzymatic protein hydrolysate of casein and pork pancreas, manufactured by Mead, Johnson & Co

protein nitrogen per kilogram of body weight were given daily. This corresponds to 2.5 or 3.75 gm of protein per kilogram of body weight, or a total protein intake for an average sized male of 150 to 250 gm of protein daily. Larger amounts, such as 1 gm of protein nitrogen per day per kilogram of body weight, are difficult to administer, and have not given us strikingly better results. Sufficient calories must be provided to free protein from all but its specific functions in the body metabolism. Not less than 20 per cent of the caloric intake should be derived from carbohydrates for maximum protein sparing action. The daily caloric intake should amount to 40 calories per kilogram of body weight, preferably more. In our experience with seriously depleted patients with chronic infections, better results were obtained when the caloric intake was raised to 70 calories per kilogram of body weight. The principle of treating protein deficiency states by a high caloric, high protein diet has been called "hyperalimentation" by Co Tui.

The most desirable way to administer protein is by *oral feeding of natural protein foods* of high biological value. Unfortunately, there are very definite limitations to what a person, particularly a sick person, will eat. The desirable amount of protein corresponds to one to two pounds of lean meat a day. A sick person has difficulty in chewing and swallowing such an amount of meat and frequently has, in addition, an aversion against protein foods. A trained dietitian can do much to overcome these difficulties. Individual attention, daily queries as to likes and dislikes, and a close check of the food actually consumed, are necessary. The mere prescription of a high protein diet is insufficient and may be misleading. Of equal, if not greater, importance is the treatment of the primary conditions which produced the state of malnutrition.

Even when this is all taken into consideration, the amount of protein food a patient will consume is usually below the desirable level. A group of 25 depleted soldiers with chronic wound infections but in fair general condition, averaged a dietary intake of 80 to 90 gm of protein a day, a few soldiers ate 120 gm of protein a day, and on rare days, up to 145 gm. Very sick patients eat only a fraction of this amount. The problem of achieving "hyperalimentation" is great and can be solved only by the use of supplementary feedings.

Methods of Supplemental Feeding ("Hyperalimentation")—Parenteral Administration.—In acute cases, where hypoproteinemia is caused by surgical shock, burn or hemorrhage, the best protein replacement therapy is whole blood and plasma. In chronic cases, however, this therapy is a very expensive one and, in addition, not too effective. To administer 100 grams of protein parenterally in the form of plasma or whole blood the equivalent of 6 pints of whole blood has to be given. The hemoglobin, although vitally important for its oxygen carrying capacity, is not utilized as food protein. Obviously, such a regimen is

impractical for prolonged use, and cheaper and more available sources of parenteral protein must be resorted to. There are now on the market four protein hydrolysate and amino acid solutions. The best known is "Amigen,"* an enzymatic digest of casein, "Amigen" is the oldest of the four products and has been well studied. There are also available two-acid hydrolysates, "Parenamine,"† and "Baxter Protein Hydrolysate Solution"‡, and lastly, there is now available a solution of pure amino acids§. These solutions are approximately one-tenth as costly as whole blood or processed plasma. They may be given in large quantities for prolonged periods of time if the following precautions are taken: (1) Absolute sterility must be observed throughout the administration, as protein solutions are ideal culture media. (2) Great care must be taken to insert and fix a 20 or 21 gauge needle properly in the vein to prevent thrombosis. We observed occasional pyrogen and depressor substance-like reactions from the use of the enzymatic digest. We have not seen such reactions with the only acid digest we have been using in any quantity, the Baxter Protein Hydrolysate. "Speed reactions," as manifested by vomiting, have not occurred in our experience when the flow was regulated at 80 to 100 drops per minute. In order to increase the caloric value of the protein hydrolysate, we recommend adding sufficient 50 per cent sterile glucose to the bottle to make a 10 per cent dextrose solution. The hydrolysates are usually 5 per cent solutions of protein digest. The pure amino acid solution contains 7 per cent of amino acids. Five hundred cubic centimeters of protein digest solution contains the equivalent of 20 gm of protein. Through the use of parenteral protein solution combined with glucose, salt and vitamins, complete parenteral feeding can be achieved for short periods of time. With unusual attention, complete parenteral feedings may be extended up to three weeks. However, rarely will this be necessary. Complete parenteral feeding has the advantage of producing complete gastrointestinal rest, equal if not superior to that induced by morphine. In general, parenteral feeding is used to supplement the oral intake in patients with severe anorexia.

Oral Administration—The second and more widely used method of supplementary protein feeding is the oral administration of protein hydrolysates or concentrated processed proteins. There are at present a number of oral preparations, commercially available, such as Amigen, Squibb Protein Hydrolysate,|| Essamine and Edamine¶. In addition to these patented products, there are edible casein and milk powder. Most of the oral protein hydrolysates have a very objectionable taste,

* Amigen is manufactured by the Mead, Johnson Corporation.

† Parenamine is manufactured by Frederick Stearns & Co.

‡ Baxter Protein Hydrolysate Solution is manufactured by Baxter Labs., Inc.

§ This solution is manufactured by Merck & Co.

|| Squibb Protein Hydrolysate is manufactured by F. R. Squibb & Sons.

¶ Edamine is manufactured by Sheffield Farms.

which is difficult to disguise. Their great advantages are their small volume and the fact that they are predigested. Amigen, for instance is highly soluble, and in combination with carbohydrates, can be made up into such a concentrated liquid that 200 cc every two hours in eight doses will provide up to 250 gm of protein and 3000 calories. If the patient objects too strongly to the taste, such mixtures can be given by gavage. The whole proteins, such as lactalbumin, casein and milk powder, are less soluble and their bulk is greater. Milk powder is the most palatable, although the bulkier of all preparations.

Special Considerations—Protein administered either parenterally or orally will cause a feeling of satiety. It is not infrequent that at the beginning of the hyperalimentation therapy, the patient will only eat the supplement and not his natural food diet. Usually with relief of the negative nitrogen balance, appetite returns. In order not to diminish the appetite, it is important to space the supplementary feedings properly, preferably during the evening period, where usually no food is served, or shortly following a meal. Five to 10 units of regular insulin, injected shortly before feeding, will create the sensation of hunger, and are valuable adjuvants in the treatment of anorexia. It should be emphasized that protein hydrolysates lack in certain essential nutrients (vitamins, minerals and essential fatty acids), and the aim of therapy is to restore the patient to a point where he can eat a highly nutritious diet of natural foods. In some patients high protein feeding will cause distention and diarrhea. This is usually transitory. In persistent cases, relief is obtained, in most instances, by slow increase of protein intake and by the use of Amphojel* or paregoric.

SUMMARY AND CONCLUSIONS

1. An outline of the current status of the subject of malnutrition is presented, with particular emphasis on protein deficiency.
2. "Protein contains the magic of life." The important role of protein in every biological process is reviewed.
3. Protein deficiency represents a common and serious complication in numerous medical and surgical conditions. The principles of diagnosis and treatment of the deficiency states are outlined.
4. Experiences are related with cases of serious malnutrition in soldiers who are chronically ill following battle trauma and resultant infection. Depletions up to one-half of the previous body weight have been noted. The "toxic loss" of protein, as demonstrated by this group is discussed.
5. The following points are emphasized: (a) Surprisingly large amounts of protein are necessary to restore the loss of body protein. (b) The ordinary hospital diet contains insufficient protein to compensate for any significant loss, there is need for supplementary protein feedings. Therapeutic aids are discussed, particularly the concentrated Amphojel is manufactured by Wyeth Inc.

trated and hydrolysed protein foods which are new and valuable adjuvants in the treatment of malnutrition

6 It is our conviction that proper treatment of malnutrition (*a*) will hasten convalescence, diminish complications and will save lives, and (*b*) can be successfully achieved even in the most stubborn cases by attention to the details discussed

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ACUTE IDIOPATHIC PORPHYRIA

Report of a Case

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Of the metabolic oddities, porphyria is particularly fascinating because of the diversity and incongruity of its manifestations. Clinically, porphyrias are separated into congenital and acute types. Congenital porphyria, with its familial occurrence and childhood appearance, is sometimes revealed by reddish discoloration of the urine and teeth, but is always characterized by photosensitivity of the skin which leads to blistering, necrosis and scarring of the exposed surfaces.¹

Acute porphyria probably also inherited but rarely showing increased light sensitivity and usually appearing in adults, is a chronic disease disclosed by acute episodes interrupting symptomless intervals of months to years. An attack may be initiated by abdominal, neurological or mental symptoms and is often accompanied by the voiding of maroon colored urine. Colicky abdominal pains, constipation, nausea, vomiting, ileus, jaundice, slight fever, leukocytosis, peripheral neuritis, paralyses, paresthesias, muscular atrophy, delirium, psychoses and convulsions have been noted to occur during an acute episode which bears a mortality rate of 50 to 90 per cent.^{2,3} The urine is not invariably red on voiding but may slowly change to a Burgundy wine color on standing in the sunlight. Watson and Schwartz⁴ have reported a simple test for the colorless porphobilinogen which, when present, is said to be pathognomonic of the disease. Acute porphyria is subdivided into acute toxic and acute idiopathic varieties. The toxic group is clinically indistinguishable from the idiopathic type and is differentiated only by the identification of a precipitating factor. Sulfonal, trional, lead, veronal, acetanilid, nitrobenzol and sulfonilamide have been incriminated.^{2,3,5}

Acute porphyria is a rare disease. Somewhat over 250 cases were reported up to 1939.⁶ It affects women more commonly than it does men, and its familial incidence has been emphasized.^{3,7,8} Waldenstrom,³ in his authoritative monograph, listed nineteen Swedish families in which there was more than one case of acute porphyria, but no case of the congenital type. He traced the disease through two to three generations and believed the defect to be transmitted as a dominant mendelian, but not sex-linked characteristic. Turner⁸ and Nesbitt⁷ also have reported cases occurring in families. The latter investigating forty-three relatives of a patient with acute porphyria, found porpho-

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bilinogen in two asymptomatic individuals adding evidence to the fact that the disease is familial, and that it may go undetected because red urine may be excreted constantly or intermittently. The recognition of such cases is of practical importance, because acute attacks have been precipitated in porphyriacs and in their unsuspected relatives by the use of barbiturates.⁸

Preceding an attack there is often a variable period of vague "neurotic" complaints. Unconvincing weakness that can be overcome by effort, anorexia, vomiting that does not interfere with eating, transient blindness and migraine headaches have been described.^{2, 8}

Extremely severe colicky abdominal pains usually usher in an acute episode. The pains may simulate ureteral or biliary colic, intestinal obstruction or appendicitis. Physical examination of the abdomen during an attack is disappointing in that there is no muscle spasm or rigidity. Constipation, which may last for days, is the rule, although in a few cases diarrhea has been reported.³ Nausea and vomiting, which may be pernicious, are commonly present. An elevation of the white blood count to 18,000, chiefly involving the neutrophils, and fever are not infrequent. Jaundice and pigmentation of the skin are noted less often, and hematemesis and melena have been reported in a rare case.³ The triad of abdominal pain, constipation and vomiting have been regarded as the cardinal symptoms of the disease. X-rays may show generalized or localized constriction or dilatation of any part of the gastrointestinal tract.^{2, 3, 8, 9} It is small wonder that many of these patients have been subjected to laparotomy. At operation, in one case, the bowel was found to be in spasm throughout its entire length.² In another case, there was extreme dilatation of the stomach and duodenum.⁹ In a third case, it was observed that blanching of the bowel repeatedly initiated intestinal spasm in localized areas.³

Of the cardiovascular manifestations, tachycardia is an almost constant finding. Heart rates as rapid as 160 have been recorded.³ Pre-cordial pain is rarely a symptom, and electrocardiographic studies usually have shown only sinus tachycardia. However, in a patient without cardiac complaints, transient T wave changes have been reported.¹⁰ These changes were associated with hypertension, but ascribed to transient myocardia ischemia resulting from coronary artery spasm. Hypertension is extremely common during acute episodes, diastolic pressures as high as 140 having been recorded.^{1, 2, 3, 7, 8, 10, 11} The hypertension is paroxysmal in character and in no case review was it persistently elevated after an attack. Angiospasm has been proposed as an explanation for the convulsions, amblyopias, hypertension, oliguria and gastrointestinal symptoms.³

Nervous system disturbances are common and may be the first and only manifestations of an attack, although often they appear when the abdominal symptoms are subsiding. Of 143 cases reported by Waldenstrom sixty had neurological symptoms.^{3, 12}

An ascending paralysis of the Landry's type has been described as typical,^{1, 14} however, in the reported cases it is extremely rare.^{8, 9, 10, 14} Acute or insidious, transient or persistent, localized or generalized symmetrical or irregularly distributed flaccid paralyses have been observed.⁸ Any of the cranial nerves may be involved, and respiratory paralysis is a frequent cause of death. Sensory disturbances are rare, but pain in the involved muscles is common. The picture may simulate progressive muscular atrophy or acute poliomyelitis, and electrical studies often show a reaction of degeneration. Visual disturbances include amblyopia and diplopia. The pupils may be either fixed and dilated or tiny and unresponsive to light. Convulsions are not uncommon and are sometimes associated with the presence of a Babinsky sign.^{8, 11} The usual investigations of the spinal fluid show no abnormalities. Various combinations of the above findings coupled with apathy, catatonia and sleep disturbances have led to a diagnosis of encephalitis lethargica. Frequently the bizarre complaints without objective findings suggest a neurosis or hysteria. Recurrent unilateral headaches are not uncommon. Psychotic disturbances of the manic-depressive, toxic or schizophrenic types may be present. There is sometimes the typical picture of a Korsakoff's syndrome. Suicide and sudden death are ever present dangers. The development of neurological symptoms is of grave prognostic significance. It connotes a mortality rate of roughly 90 per cent.⁸

The relation of the defects in porphyrin metabolism to the symptomatology and pathology is not clear. Direct application of porphyrins to the bowel produces a spasm unrelieved by atropine.¹ Clinically, however, although the abdominal symptoms abate, the excretion of porphyrins may continue unaltered. Mason and his associates² have described degenerative changes in the autonomic ganglia, particularly the celiac, and believe this to be the explanation of the gastrointestinal disturbances. Intracellular pigment deposits and cirrhosis have been reported in a few cases and may account for the jaundice which is sometimes present.^{1, 2, 8} Oliguria and convulsions have been attributed to transitory changes in the blood vessels, however, in three cases, there were inflammatory and necrotic changes in the renal arterioles, and in another case there was both clinically and pathologically periarteritis nodosa.³ The appearance of severe multiple neuritis during a course of treatment with hematoporphyrin hydrochloride has been used as evidence of the toxic neurotropic effects of the porphyrins.¹⁶ Widespread but patchy degeneration of the myelin sheaths and axon cylinders predominantly involving the motor nerves has been described.⁷ Nerve cell degeneration has been found also in the cerebral cortex, basal ganglia, cerebellum and spinal cord. These changes might well explain the varied neurological and mental manifestations of the disease. Although the color of the urine, which varies from brown to red depending upon the pH, is often attributed to the presence of

porphyrins, other pigments may account for a good part of the abnormal coloration^{1 2,3,7,20}

Porphyria has been likened to gout³ In both diseases a characteristic symptomatology and metabolic defect are recognized, but in both the relation of the chemical abnormalities to the acute clinical manifestations remain obscure Discussions of the chemistry and metabolism of the porphyrins and their relation to the porphyrias and other diseases may be found in the reviews of Watson,¹ Mason,² Waldenstrom,³ Nesbitt,⁷ Harbittz,¹⁰ Dobriner²⁰ and Welcher²¹

REPORT OF A CASE

HISTORY—A 45 year old married soldier with 18 years' Army service was transferred to the neurological ward of Halloran General Hospital on September 12, 1945, with the complaint of weakness and pains in the arms since July 22, 1945

The family history revealed that his mother was found dead at the age of 30 without any explanation Her death and the sudden death of his 40 year old brother were never explained

The only suggestive evidence of any previous difficulties, sifted from an otherwise negative past history, was that fourteen years prior to admission he had had a severe attack of abdominal cramps which cleared suddenly and completely after a day Again in November, 1943, while working in Oran, Africa, he had had recurring bouts of abdominal pain and diarrhea requiring hospitalization Repeated stool examinations were negative, and the difficulties disappeared spontaneously in a few months He denied taking any medication

The present illness began about a year before entry Although able to continue working at telephone line construction, he lacked his usual energy His appetite became capricious, and a breakfast of bacon, eggs, toast and coffee sufficed for each day Once or twice a month a craving for sweets was satiated by eating a pound or two of chocolates at a time His weight, although checked frequently, did not deviate from the usual 160 pounds Nine months ago he noted shortness of breath on exercising or lying flat and began sleeping with his head elevated Roughly six months ago hoarseness appeared, and on one occasion, about the same time, he noted that his urine was orange colored On June 15, 1945, while walking to work he suddenly became very short of breath and was seized by an excruciating pain directly below the left nipple Perspiring and weak, he rested until the pain abated in half an hour He walked to the dispensary, was seen by the medical officer and returned to work Four days later after scaling up a 14 foot pole, he had a similar episode, with knifelike left chest pain and dyspnea When the attack subsided, he returned to the dispensary and immediately was put to bed

PHYSICAL EXAMINATION—In the admission note on June 19, the patient was described as being a well developed, slightly obese, ruddy faced male with dyspnea and mild orthopnea Wheezing rales were heard throughout the chest The respiratory rate was 24 per minute The heart was not enlarged, was rapid (100), but regular with good quality heart sounds The blood pressure was 155/112 The abdomen was not remarkable There was no venous distention in the neck The remainder of the examination was essentially negative The oral temperature was 99.2° F

LABORATORY DATA—Red blood cells, 4.8 million per cubic millimeter, hemoglobin, 90 per cent Sahli, white blood cells, 7300 per cubic millimeter, neutrophils, 61 per cent lymphocytes, 33 per cent, eosinophils, 4 per cent Urine specific gravity, 1.024, amber color, no protein, sugar or acetone Sedimentation rate 8 mm per hour Electrocardiogram T waves were notched in Lead II and inverted in Lead III (Fig 65)

The patient was thought to have an acute posterior myocardial infarction with incipient cardiac failure.

COURSE IN THE HOSPITAL.—The patient was confined to bed and treated as a case of acute coronary occlusion. Sodium pentobarbital 0.1 gm., was used each night as a sedative. On June 22 after drinking a glass of ice water he developed marked dyspnea, a feeling of tightness in the chest and pain involving the left side of the body. He became cyanotic, and his blood pressure was 105/65. Morphine sulfate was required for control of the pain. On the following days the

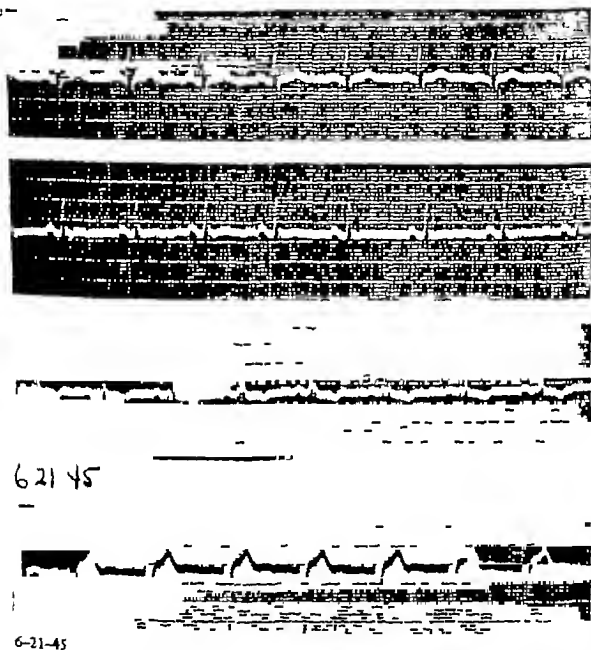


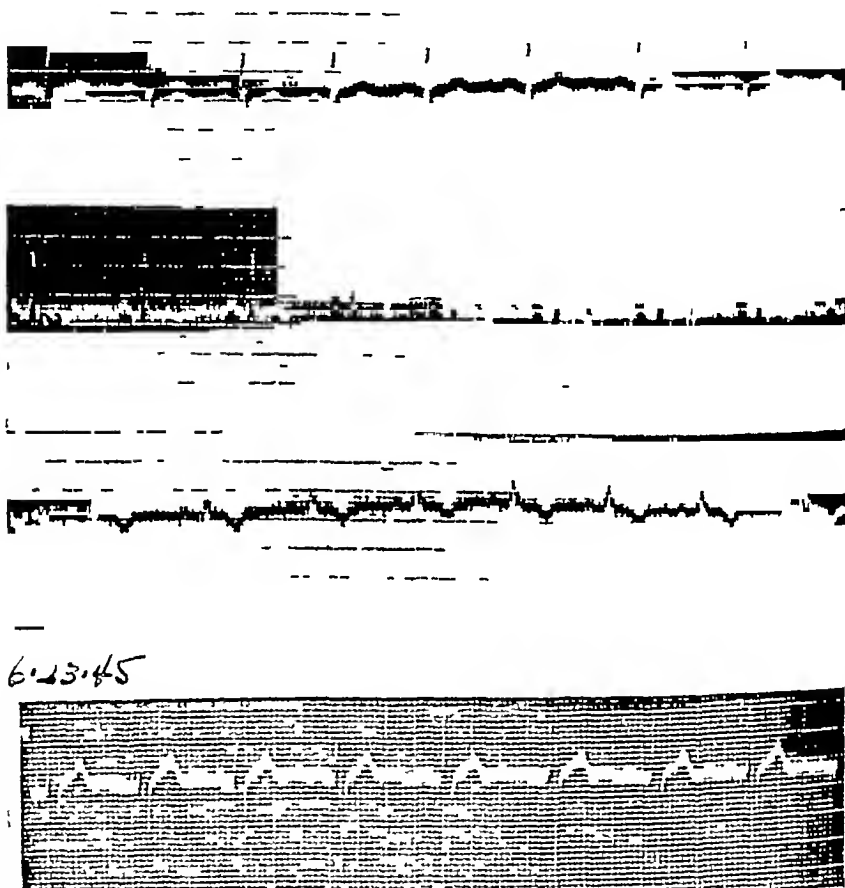
Fig 65—Electrocardiogram taken June 21 1945 revealing low voltage notched T waves in Lead II inverted in Lead III

blood pressure varied from 150/110 to 110/70. Serial electrocardiograms were taken. The T waves became diphasic in Lead II and deeply inverted in Lead III but in subsequent records they returned to the upright position in both leads (Figs. 66, 67).

Gastrointestinal symptoms, however, dominated the picture. The patient had persistent constipation and bouts of abdominal pain. In the week prior to July 19 he had no bowel movements, and all manner of enemas were unsuccessful. Repeated examinations of the abdomen showed only audible peristalsis and diffuse

tenderness without muscle spasm or rigidity. The blood count remained unaltered until July 19, when the white blood count rose to 13,200 per cubic millimeter and the sedimentation rate increased to 20 mm per hour. The urine on June 23 was recorded as dark amber in color. On the four subsequent reports the urine was described as "red" or "red-brown" in color with negative tests for protein, blood and bile.

The patient began to vomit and suffer from abdominal distention on July 16. The following day x-rays were taken and reported as follows: "A survey film of



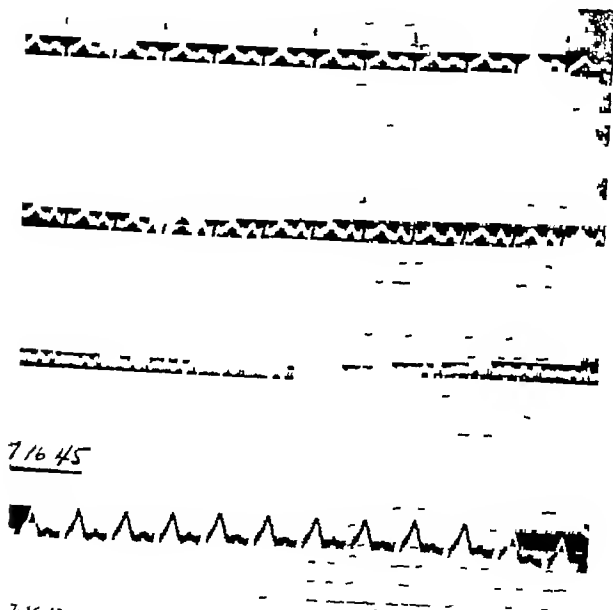
6-23-45

Fig 66—Electrocardiogram taken June 23, 1945, showing inversion of T waves in Leads II and III

the abdomen shows distention of loops of small and large bowel by gaseous content. In the erect position, numerous fluid levels are scattered throughout the abdomen, chiefly on the left side (see Fig 68). Barium enema studies show just distal to the sigmoid a persistent narrowing of the large bowel which could not be overcome during the course of the examination. The barium could be forced beyond the area of narrowing, but could not be driven beyond the hepatic flexure. Following evacuation, a small amount of barium has entered the ascending colon and cecum, and although not well demonstrated, there appears to be some nar-

rowing of the large bowel just distal to and perhaps including the hepatic flexure impression. From this examination it appears that there was obstruction in the large bowel in the region of the hepatic flexure. The possibility of another obstruction just distal to the sigmoid cannot be excluded.

On July 19 under procaine spinal anesthesia, the cecum was exteriorized but not opened. Abdominal exploration was not carried out because of the patient's poor general condition. The day after operation he was passing flatus and soon was having irregular spontaneous bowel movements.



7-16-45
Fig. 67—Electrocardiogram taken July 16, 1945. The T waves are upright in Lead II and flat in Lead III.

Four days after operation he was described as being delirious and at times irrational. For the next three days he appeared desperately ill with repeated attacks of dyspnea and precordial pain which required morphine frequently and an oxygen tent continuously. The heart was accelerated out of proportion to the oral temperature of 100° F. The blood pressure was 100/70 but the skin was warm and moist. The venous pressure was 4 cm. of water. The decholin arm to tongue circulation time was 18 seconds. An x ray of the chest was not remarkable. The urine continued to be red.

Hoarseness was first noted on July 24. Three days later there was generalized weakness, and the deep reflexes could not be obtained in the upper appendages. The patient could not touch his nose with his right hand and had a coarse resting tremor of both hands as well as hyperesthesia over both feet. These events were elaborated by the patient. He said that following the operation he became progressively weaker, so that at one time he was unable to sit up or move either hand. Both arms and the right leg were most affected by the weakness. The involved muscles ached and the pain was made worse by being moved or by trying to move. About the same time the soles of his feet and his toes became excruciatingly sensitive. The touch of the bedclothes was agonizing. Both the muscle soreness and skin sensitivity have gradually subsided.



Fig. 68—Scout film of the abdomen taken in the upright position showing gaseous distention of the bowel and numerous fluid levels.

On July 28 the exteriorized cecum perforated spontaneously. In mid August, however, he had improved so much that he was able to sit up in a chair although marked atrophy of the arm and shoulder musculature was recorded for the first time in the daily progress notes. A lumbar puncture was done on August 16 showing normal dynamics, a clear colorless fluid with 40 mg of protein, no cells, 79 mg of sugar, negative Wassermann and no elevations in the gold curve. Plasma proteins, icterus index, van den Bergh, bromsulfonphthalein test, basal

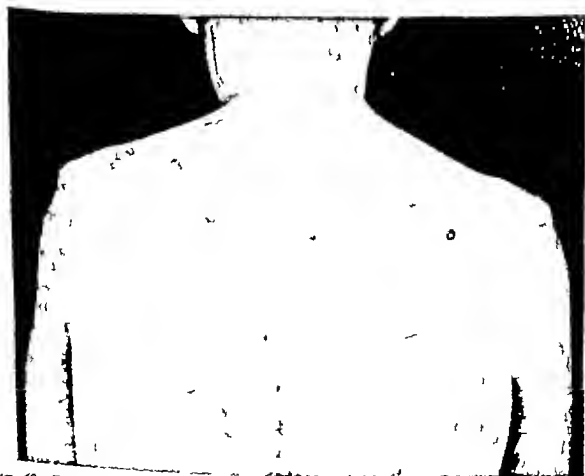


Fig 69—Pictures showing pronounced deltoid atrophy and lesser wasting of the suprascapular and infrascapular muscles.

metabolic rate, carbon dioxide combining power, blood calcium, phosphorus, urea and fasting sugar were not remarkable.

ADMISSION TO HALLORAN GENERAL HOSPITAL

The patient was brought to Halloran General Hospital August 31, 1945, with the diagnosis of acute posterior myocardial infarction complicated by paralytic ileus, cecal fistula and infectious polyneuritis. On the surgical service, the gastrointestinal x-rays were repeated and showed only a small functioning cecostomy. A laryngoscopic examination revealed the left vocal cord to be paretic and fixed in the adducted position. He was transferred to the neurological ward on September 12.

PHYSICAL EXAMINATION—Physical examination at that time showed the patient to be a thin, wasted, ruddy faced man with marked muscular atrophy about the shoulders (Fig. 69). There was no abnormal pigmentation or roughening of the skin. The right palpebral fissure and pupil were smaller than were those on the left. There was a slight enophthalmos on the right side. Marked arcus senilis was evident, but there were no abnormalities in the pupillary or extraocular movements. The optic fundi were not remarkable. The nasal septum was intact. The tongue, of good color and showing no papillary atrophy, did not deviate from the midline on protrusion. The uvula showed no deviation on elevation. No venous distention was noted in the neck, and the lungs were clear. The heart was not enlarged. The rate was 120, slowing evenly on carotid pressure. No murmurs, arrhythmias or abnormal sounds were detected. The radial pulses were equal, and the pedal pulses were felt easily. The blood pressure was 130/85. The abdomen was slightly distended. There was a right lower quadrant cecostomy. No organs or masses were felt, and peristalsis was audible. The remaining positive findings were confined to the neurological examination.

NEUROLOGICAL EXAMINATION—The patient was intelligent and cooperative, displaying proper affect and attention. He was oriented and had no memory defects or hallucinations, however, mentation was slowed. Examination of the cranial nerves revealed no abnormalities other than those mentioned above: small pupil, enophthalmos and diminished palpebral fissure on the right and paretic left vocal cord. It is possible that the tachycardia and continued bowel dysfunction were stigmata of vagal imbalance. The only sensory disturbance was hyperesthesia over the soles of both feet. There was generalized weakness, which made it difficult for the patient to sit up or walk. Lying on his back, he could not bring himself to a sitting position without turning to his left side. Flaccid paralysis and profound wasting of the deltoids, supraspinatus and infraspinatus muscles were approximately equal on the two sides. Lesser atrophy and weakness, out of proportion to the general debility, symmetrically involved the biceps and triceps brachii, latissimus dorsi, pectoral and teres groups. Myoedema was demonstrable, but no fasciculations could be detected. The arms hung limply to the sides. The patient could not flex, abduct or rotate the arms, although there was no limitation of shoulder joint mobility. Extension and abduction were performed weakly as were all the movements of the forearms and hands. There was diminished strength in both lower appendages, which was more marked on the right. The heel-to-knee test was done well bilaterally and there was a coarse tremor of both hands on voluntary movement. No deep reflexes were elicited in either upper extremity. The knee kicks and ankle jerks, although diminished, were about equal on the two sides. The corneal and abdominal reflexes were lively but neither cremasteric reflex was obtained. No Gordon, Oppenheim, Rossolimo, Babinsky or Hoffmann sign was elicited.

LABORATORY DATA—The latest blood study showed a hemoglobin of 13.6 gm per 100 cc and a white blood count of 6150 with normal distribution. The freshly voided urine on one occasion was port-wine colored. On another occasion, it

was clear and yellow. The latter tested by the method of Watson and Schwartz, was positive for porphobilinogen. A portion of this same specimen was set aside in the sunlight and within six hours it had changed to a reddish brown hue. Red fluorescence was shown in a Wood's light by the sodium hydroxide precipitate of the urine redissolved in hydrochloric acid indicating the presence of porphyrins.

Examination of the urine graciously done by Dr. C. J. Watson revealed the following: 156 gamma of Type I coproporphyrin and 2340 gamma of uroporphyrin were excreted each day. The uroporphyrin was further identified as a combination of a large amount of Type I and a small amount of Type III isomers.

Comment—The unexplained death of the patient's mother and brother early in adult life is suggestive of a familial disorder. Sudden death in acute porphyria has been described. The urine of the only available relative of the patient, his daughter, showed no porphobilinogen.

The case presented the usual features of the disease with a nebulous period of ill health preceding an acute episode with abdominal pains, constipation, red urine and later appearing paralysis. The presenting complaints of precordial pain and dyspnea associated with electrocardiographic changes are extraordinary. Paroxysmal hypertension, which is quite common, was also observed. The true nature of the patient's illness was missed because the only diagnostic feature of the disease, the red-colored urine, was not appreciated.

Whether the continued use of sodium pentobarbital in the hospital altered the patient's course is difficult to evaluate. In the light of the present knowledge, all barbiturates are contraindicated. Attempts to control the abdominal pain in other patients with intravenous calcium gluconate have met with varying success.^{6, 8} Large doses of niacin,¹³ injections of liver¹ and the use of diuretics³ have been tried with equivocal results. The patient's course seems little altered by the liberal use of vitamins and injections of crude liver over a period of weeks.

The patient at present weighs 124 pounds and is slowly regaining the use of both arms. The deep reflexes in the upper appendages are obtainable. His appetite is poor and constipation continues to be a problem. For a period of a week he had sacral anesthesia, which has completely cleared. He is no longer bothered by abdominal pains. The freshly voided urine varies daily from a straw color to a cherry red.

SUMMARY

- 1 The clinical features of acute porphyria are reviewed.
- 2 Attention is called to the not uncommon finding of paroxysmal hypertension in the disease.
- 3 A case presenting atypical features of precordial pain with electrocardiographic changes is reported.
- 4 The only diagnostic feature of the disease, the red-colored urine, is stressed.

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citis was not believed to be present. The severity of the pain required morphine which was repeated twice in about 24 hours before the acute abdominal episode subsided. He recalled that on March 19 he had acted oddly and had been confused and delirious. His memory for events during the next ten days was patchy but he recalled visual and auditory hallucinations as well as delusions. For a period of three to four days after this episode he was mentally clear and ate well. He then started to notice generalized weakness which rapidly became worse until April 16 when he developed pneumonia of the right lower lobe. During this time he had a dysphonia with a weakened and squeaky type of voice. After chemotherapy failed to produce a rapid response, atelectasis of the lung was suspected and confirmed by x-ray. He was given supportive therapy until he regained more strength and on May 16 a bronchoscope was passed and a mucous plug removed from the right lower lobe bronchus. During this severe illness he became very weak and lost about 50 pounds, despite a hearty appetite. He could not move out of bed, raise his arms or effectively use his hands. He was later evacuated to the States and arrived at this hospital on June 14, 1945.

The family history and past history are noncontributory. At no time prior to his illness was he taking any medicine, since he was engaged in active combat.

PHYSICAL EXAMINATION—This patient showed severe emaciation with generalized muscular weakness. His weight was 106 pounds, blood pressure 110/70, pulse 92 and temperature 97.4° F. The skin was deeply pigmented but the oral mucosa was free of pigmentation. There was a large keloid on the right lower quadrant where the patient had scratched during his acute psychotic state. Examination of the eyes, ears, nose and throat revealed nothing abnormal. Laryngoscopic examination failed to show any paresis of the vocal cords despite the presence of dysphonia. The heart rhythm was regular but the basal sounds were somewhat weak. Examination of the lungs was essentially normal except for evidence of some pleural thickening at the right base posteriorly. The abdomen was scaphoid and no viscera were palpable and the genitalia and anorectal area were within normal limits. Neurological examination revealed normally active reflexes, no sensory changes, and no pathological signs. The abdominal reflexes were absent. There was marked atrophy with dysfunction of the muscles of the shoulder girdle including the spinati, serrati, deltoids and lower trapezi (Fig. 70), and there was a severe symmetrical bilateral paresis of the extensor digitorum communis, extensor indicis, extensor pollicis brevis and longus, with the fourth and fifth digits most affected, producing a clawhand appearance.

LABORATORY DATA—Red blood cells, 4,250,000, hemoglobin, 84 per cent, leukocytes 7200 with 52 per cent neutrophils, 47 per cent lymphocytes and 1 per cent basophils, no basophilic stippling. The Kahn test was negative. The fasting blood sugar was 85 mg, nonprotein nitrogen 25.4 mg and chlorides 447 mg per 100 cc. The urine was straw in color, with a specific gravity of 1.022, acid reaction, no sugar or albumin, and a strongly positive test for porphyrin and its precursor porphobilinogen. The spinal fluid was normal and negative on test for porphyrin. X-ray of the chest showed some residual pleural thickening at the right base adjacent to the diaphragm.

COURSE IN HOSPITAL—The patient was put on a high caloric, high vitamin diet with supplementary vitamins. Early motion of all muscles was encouraged and physiotherapy was instituted immediately. This consisted of daily heat, massage, and passive exercise of the involved muscles. Within ten days the patient was freely ambulatory. A slow, steady gain in weight was evident from week to week together with a gradual return of muscle volume and function in the shoulder girdle. The patient was allowed out on pass but was cautioned against overexposure to the sun. Several urine specimens were allowed to stand overnight on different occasions, but in none of them was any abnormal color detectable. On August 6, 1945, a twenty-four hour specimen of urine was collected for a quanti-

tative lead estimation. For the first time a light red color was seen in the urine (The patient admitted that he had exposed himself to the hot sun during the

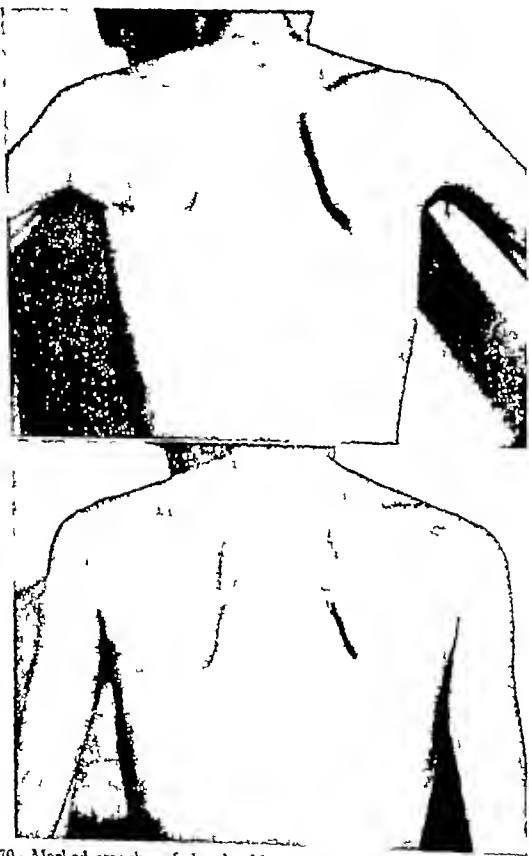


Fig. 70.—Marked atrophy of the shoulder girdle is evident. Taken approximately four months after the onset of illness.

previous day for about four hours.) This specimen contained no lead but was positive for porphyrin, containing 33.8 micrograms of ether soluble porphyrins per 100 cc. of urine. A short course of prostigmine therapy produced no immediate

clinical improvement. In a short time the dysphonia disappeared and the abdominal reflexes returned. The patient was then sent on sick leave. An examination made upon his return, six months after the onset of his illness, disclosed a total weight gain of 20 pounds since his admission. There was about 90 per cent return of muscle function and volume in the shoulder girdle, except for the rhomboids. The latter exhibited about 75 per cent return with an accompanying slight winging of the vertebral borders of the scapulae still evident. The muscles of the hands gave evidence of up to 25 per cent recovery, greater on the left.

The patient continued to gain weight and strength. Electric shock stimulation of the small muscles of the hand was instituted and within two weeks about 15 per cent further recovery in the strength of these muscles was observed.

On October 18, 1945 he complained of aching in the lumbosacral area, but examination was negative. He stated that on October 21, 1945 he had a sudden "stitch" in the right lower quadrant lasting a few moments. The urine was examined the next day and appeared grossly to have a pinkish tint. About 10 cc of this urine which was previously acidified with concentrated hydrochloric acid was exposed to ultraviolet rays for about 90 seconds in an open dish. It then assumed a definite red color. The same reaction was observed after exposure of the urine to sunlight.

Other than these minor exacerbations the patient has felt progressively better and it is expected that further improvement of his muscular atrophy and paresis will be observed in the near future.

Summary—This is the case of a 26 year old officer who, under the strain of combat exhaustion, developed acute abdominal pain followed by a short-lasting psychosis and a subsequent acute muscular atrophy of the shoulder girdle with marked symmetrical paresis of extensor muscles of the fingers. His urine gave a positive test for porphyrin approximately three months after the onset of his illness, again after four and one-half months following exposure to the hot sun, and finally seven months later following an attack of abdominal pain. The patient has made very satisfactory progress in his recovery from the neurological complication.

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* Since this case was presented, the patient has continued to pass a pinkish colored urine almost daily (January 26, 1946).

THROMBOCYTOPENIC PURPURA FOLLOWING RUBELLA

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DURING the present war there has been an opportunity to observe and study the acute infectious diseases in larger numbers than usually is afforded in civilian life. The appearance of complications of these diseases increases proportionately with the number of cases observed. It seems of clinical importance therefore to report the occurrence of a rare complication of one of the more benign infectious diseases, thrombocytopenic purpura following rubella.

Thrombocytopenic purpura during or following the course of the acute exanthemas has been noted infrequently. It has been reported following scarlet fever,¹ varicella,² measles,³ and rubella.⁴ There have been cases associated with upper respiratory infections⁵ and infectious mononucleosis.⁶ Its appearance complicates the course of the associated illness and may assume the major problem of therapy in such infections.

The clinical findings are a result of bleeding into the skin, mucous membranes and tissues. The onset is noted usually as a purpura of the skin or sudden epistaxis and bleeding gums. These symptoms are followed by hematuria, melena and in some instances by cerebral bleeding. The spleen may or may not be palpable. The blood picture, in addition to the lowering of the blood platelets, may show a normocytic anemia depending upon the severity of the bleeding. The bleeding time is prolonged, the tourniquet test is positive and the clot retraction is slow.

Two cases of rubella complicated by thrombocytopenic purpura are reported.

CASE I—This 28 year old white soldier was admitted to the hospital on February 20, 1943 because of a rash. He had an injected pharynx without Koplik spots, a generalized macular rash and postauricular and posterior cervical lymphadenopathy. A diagnosis of rubella was made. He did well until February 22 when he began to have epistaxis and later the same day oozing from the posterior pharynx and the buccal and gingival mucous membranes. Numerous petechiae were found on his skin. A Rumpel Leede test was strongly positive.

His bleeding tendency continued and on February 23 he had a platelet count of 40,000 and bleeding time of thirty minutes (Fig 71). On the 24th gross hematuria and intestinal bleeding became manifest. On this date the spleen was palpable two fingerbreadths below the costal margin. The urine gradually became normal, the stools assumed a normal brown color and all active bleeding manifestations ceased within two weeks. Some remnants of purpura of the skin remained

From Fort Jay Regional Hospital, Governors Island, New York

for twenty-six days but after this there were no further evidences of bleeding. At this time the blood platelets were still less than 100,000 per cubic millimeter but they soon rose to a normal level. Two transfusions of 500 cc each of fresh citrated compatible blood were given during the time when he was bleeding actively.

He was transferred to another hospital for convalescence on March 30, 1943. His last studies at that hospital in July, 1943 revealed a platelet count of 429,000 per cubic millimeter and a bleeding time of one and one-half minutes. There had been no purpuric manifestations of any kind. He was discharged to full duty on July 28, 1943.

CASE II—This patient, an 18 year old white soldier, was admitted to another hospital on February 25, 1945 for treatment of an atypical pneumonia from which he made an uneventful recovery. On March 15, 1945 while on a furlough at home he developed fever, malaise, sore throat and bilateral cervical adenopathy. When readmitted to the hospital a generalized macular rash was noted and a diagnosis

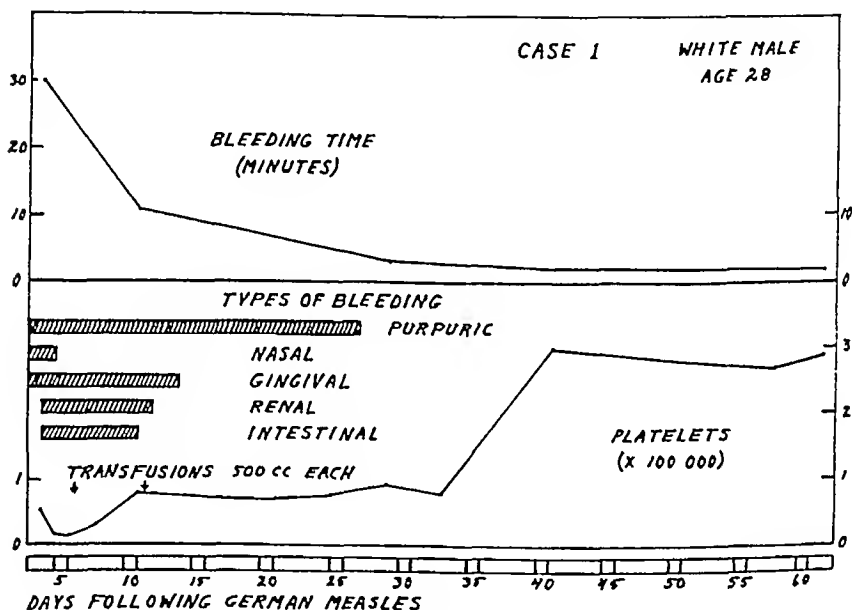


Fig 71

of rubella made. Four days later it was apparent that the rash had given way to a generalized purpura and the mucous membranes were studded with petechiae. Severe epistaxis ensued which required nasal packing. Blood studies were completely normal except for a platelet count of 30,000 and a bleeding time of 85 minutes. A Rumpel-Leede tourniquet test revealed 50 petechiae per square inch. The blood prothrombin time was normal. During the next few days the patient developed marked bleeding from the gums and gross hematuria. He was transferred to this hospital for further observation and treatment.

Blood studies revealed complete absence of platelets and prolongation of the bleeding time to thirty-four minutes. There was no clot retraction in forty-eight hours. The spleen was palpable two fingerbreadths below the costal margin. The patient was given six transfusions of fresh citrated compatible blood with out apparent alteration of the picture of generalized bleeding. The severity of the hematuria was particularly striking. The urine had the gross appearance of blood. Using ordinary technic for counting red blood cells, the urine at one

time showed 1 150,000 red cells per cubic millimeter and a hematocrit reading of 17 per cent. The patient complained of marked frequency urgency, dysuria and pain in the bladder region. Frequent doses of antispasmodic bladder mixture and codeine gave but little relief.

On March 29 1945 after persistent gross hematuria for one week, the platelet count had increased to 76 000 and the hemorrhagic manifestations disappeared within a few days. The platelet counts and bleeding time approached normal values at a very gradual rate (Fig 72). In fact, fifty days after the onset of purpura, the platelet count was still 67 000 and the bleeding time 8.5 minutes. The patient made a complete recovery and was discharged to a convalescent hospital on April 30, 1945 at which time the platelet count was 208 800 and the bleeding time two minutes and forty seconds. The 14 per cent magnesium sulfate slide method was used for counting platelets in both cases.

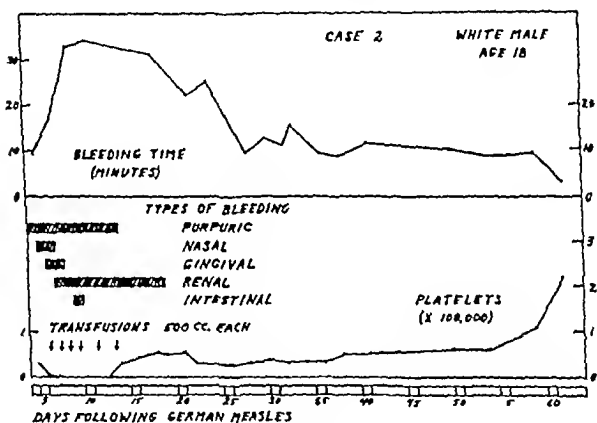


Fig 72.

Comment.—These two cases of typical rubella occurred in young individuals during known epidemics of this disease. Both patients gave a negative family history and a negative past history of bleeding tendencies. There was no history of allergies. Neither had had medication just prior to or during the course of the rubella.

Cases of thrombocytopenic purpura associated with infections are regarded as secondary or symptomatic in type in contrast to the idiopathic or essential type. The reason for the selective action against the blood platelets is obscure though the rarity with which it occurs in these common diseases is suggestive of an individual susceptibility to the agent causing the original disease.⁸ Therapy is supportive with the treatment of blood loss by transfusions and the local applications of styptics to accessible bleeding surfaces. Fresh blood appears to be

better than stored blood for transfusion^{6,7,8} Both of our patients received fresh citrated blood with benefit The prognosis with such therapy is excellent There was no evidence in either of our cases of any increase in the available circulating blood platelets after transfusion This finding suggests that the transfusions are of value because of the replacement of the circulating red cells The complete return of the blood platelets to normal requires a prolonged period of time though the bleeding tendencies subsided when the blood platelets were as low as 50,000 It is important to recognize benign infections as a cause of this rather alarming clinical picture because of the favorable prognosis and because of the benefits of supportive therapy

SUMMARY

1 Two cases of thrombocytopenic purpura following rubella have been reported

2 The importance of recognizing the occurrence of this complication following infectious diseases is stressed

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PENICILLIN THERAPY IN THE MANAGEMENT OF THE PYODERMAS AND SECONDARY PYODERMIC INFECTIONS

Report of Seventy Cases

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THIS is a report on the local and parenteral antibacterial action of penicillin in the treatment of dermatologic entities etiologically pyogenic, such as ecthyma, furunculosis, impetigo contagiosa, sycosis vulgaris and infectious eczematoid dermatitis, and of secondary pyogenic infected dermatologic diseases, such as acne vulgaris with infections of the cystic lesions, and dermatophytosis with complicating cellulitis.

Practically all of the seventy patients under consideration were evacuated from the South Pacific, Southwest Pacific and European theaters, primarily because of their dermatologic diseases. The only entities showing considerable incidence in the continental United States in our series were impetigo, sycosis vulgaris and secondary cellulitis with dermatophytosis of the feet, and in each of these categories about 40 per cent of the cases originated here. The patients evacuated from the overseas theaters showed loss of weight varying from 10 to 30 pounds.

All of the cases were of the chronic, recurring type, resistant to ordinary types of therapy. Only local therapy had been employed such as wet dressings (Burow's, saline, boric acid and potassium permanganate solutions), and various aniline dye topical applications (gentian violet, etc.), as well as pastes and ointments (ammoniated mercury, resorcin and sulfur). A few patients had been using sulfadiazine or sulfathiazole ointment (5 to 10 per cent) without curing the disease. None of our patients had received penicillin locally or intramuscularly, with the exception of several with severe acne vulgaris who had received one or two courses of one million units of penicillin sodium intramuscularly.

Cultures of the discharges or exudates in all cases showed various staphylococcal infections. The hemolytic staphylococci, all coagulase-positive, were the sole infecting organisms in all of our cases of cystic acne, of secondary cellulitis and of furunculosis as well as in both cases of infectious eczematoid dermatitis constituting slightly over 60 per cent of the predominating infecting organisms in our series.

THERAPY

Local topical continuous wet dressings, consisting of penicillin sodium in sterile gauze, 250 units per cubic centimeter in normal saline, were applied in all cases except those of acne vulgaris. A fresh solution was prepared every twenty-four hours. Usually a pint daily was sufficient except in the cases of infectious eczematoid dermatitis which required from two to three pints daily. Treatment usually was carried out for three to five days, but in the cases of infectious eczematoid dermatitis the local medication was used for from ten to fourteen days. In six cases of furunculosis, two cases of sycosis vulgaris, both cases of infectious eczematoid dermatitis and all the cases of acne vulgaris, one million units of penicillin sodium were given intramuscularly (25,000 units every three hours).

All patients who had lost a considerable amount of weight were given diets of 5000 calories per day. The patients suffering from acne and furunculosis were given the same diet because of loss of weight.

TABLE 1 —DURATION OF THE DISEASES AND THE NUMBER OF CASES EVALUATED

	Duration of Disease	No. of Cases
Ecthyma	12 to 18 months	7
Furunculosis	8 months to 2 years	10
Impetigo contagiosa	2 weeks to 2 months	10
Infectious eczematoid dermatitis	1 case 6 months 1 case 2 years	2
Acne vulgaris, severe, cystic	Average of 10 years with repeated exacerbations in the past 2	21
Cellulitis (dermatophytosis)	Intercurrent, acute	10
Sycosis vulgaris	6 to 24 months	10

although some of the patients objected to the rich diet since they had been told that acne or "boils" "does bad" on a rich diet.

The urinalyses, red and white blood cell counts in all cases were within normal limits. The cases of acne and furunculosis showed fasting blood sugars within normal ranges.

Ecthyma—There were seven cases of recurring ecthyma, all of them of more than twelve months' duration, all on the lower extremities, especially on the lower third of the legs, both anteriorly and posteriorly, and about the ankles, more so on their outer aspects, about the bony prominences where friction was most apt to occur. Many residual, irregular, depressed scars with either depigmentation or slight surrounding hyperpigmentation were present at the sites of the former lesions. The ecthyma lesions were from dime size to quarter size, crusted, pustular and serum-oozing, and surrounded by a variable amount of inflammatory cellulitis. Of the seven cases, five were from the South Pacific and Southwest Pacific theatres, and two were from the European theater of operation. Penicillin was employed as a local

wet dressing after the crusts had been removed by saline soaks and gentle forceps manipulation if required. All cases healed rapidly although the patients required further hospitalization for complete resolution of the lesions and firm scarring to take place.

Furunculosis—Of the ten cases, eight came from the Pacific theaters and two from the European theater. Since all of our cases were generalized and of long standing, both local and intramuscular therapies were given. Where the furuncles were large, easily accessible and few in number, local wet dressings were applied for three to five days with considerable local improvement in a short time. Pain and swelling, erythema and resolution of the involved lesions occurred definitely to a degree greater than and more rapidly than with the ordinary type of

TABLE 2.—THE PREDOMINATING CAUSATIVE ORGANISMS AND THE THERAPY EMPLOYED IN EACH DISEASE

Disease	No of Cases	Organism Present	Penicillin Therapy
Ecthyma	7	Staph. albus	250 U in 1 cc. saline locally
Furunculosis	10*	Hem. Staph.†	250 U in 1 cc. saline locally 1 000 000 U intramuscularly
Impetigo	10*	Staph. aureus	250 U in 1 cc. saline locally
Sycosis vulgaris	8	Staph. albus	250 U in 1 cc. saline locally
	2	Staph. aureus	1 000 000 U intramuscularly
Infectious eczematoid dermatitis	2	Hem. Staph.†	250 U in 1 cc. saline locally 2 000 000 U intramuscularly
Acne vulgaris	21	Hem. Staph.†	1 000 000 U intramuscularly
Cellulitis (dermatophytosis)	10	Hem. Staph.†	250 U in 1 cc. saline locally

* Six cases received both local and intramuscular therapy and four cases were given penicillin intramuscularly only.

† All *Staphylococcus hemolyticus* organisms were coagulase-positive.

wet dressings. In this type of case (four treated), no penicillin was given.

In the patients receiving penicillin intramuscularly, in addition to local therapy, only slight improvement of the lesions was noted. It was our opinion that these patients had a low opsonic index for the culpable organisms and therefore the antibiotic effect was of very short duration. An important factor in the cases of furunculosis was a severe generalized hyperhidrosis, especially affecting those patients coming from the Pacific theaters.

Impetigo Contagiosa—There were ten patients with this condition in which *Staphylococcus aureus* was cultured. Local therapy was employed and in three to five days healing was complete. No relapses or complications were noted. All cases were relatively acute and recent. Five of the more chronic cases were from the European and Pacific theaters while the remainder were local cases.

Contraindications and Reactions to Penicillin Therapy—We found no contraindications to the use of penicillin sodium either locally or intramuscularly, and there were no complications therefrom. There were no cases attended by toxic reactions or severe local disturbances. No cases of sensitization to penicillin sodium were noted, although subsequently in another series of cases urticarial reactions and a vesicular dermatitis of the hands were noted and were believed to be due to this agent.

Since the epidermis of many persons is known to be sensitive to pathogenic skin fungi and some saprophytic types and their products, it may be expected that local reactions will occur, and they should be suspected when an eczematous process expands under penicillin therapy.

SUMMARY

1 Penicillin sodium is an effective agent in the treatment of pyogenic infections as listed above, and in these cases is more effective than ordinary wet dressings.

2 The hemolytic staphylococcus and *Staphylococcus aureus* and albus skin infections respond to penicillin sodium therapy, both locally and parenterally, with good to fair results. Best results were obtained in secondary cellulitis, impetigo, ecthyma and infectious eczematoid dermatitis. Less favorable results were obtained in cases of acne vulgaris with infected lesions, and sycosis vulgaris.

3 Toxic reactions had not been observed with either local or intramuscular treatments.

4 Penicillin sodium has no effect upon acne vulgaris or dermatophytosis, except on the secondary infections. We believe it should not be used in uncomplicated cases of acne vulgaris or dermatophytosis.

AMEBIASIS CUTIS

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AMEBIC invasion of the skin is a rare complication of intestinal amebiasis, but since it is a serious complication, since it may be the only clinical evidence of the disease and since it is curable if diagnosed, it is considered worthwhile to report an additional case and review the literature on this subject. Such a review is timely because of the frequency of amebiasis in troops overseas, some of whom may develop the complication years after their return to civilian life

HISTORY

The ameba was discovered in 1755 by August Johann Roesel von Rosenholf. It was first named "amiba" in 1822 by Baron de Saint Vincent and changed to "amoeba" by Ehrenberg in 1830. It was found by Lamb in 1860 and by Lewis in 1870 to be a cause of dysentery. In 1891, Councilman and Lafleur introduced the term "amebic dysentery." In 1903 Schaudinn distinguished two types of entamoebae: one he called "*Entamoeba histolytica*" because it ingested tissue and red cells, and the other, a nonpathogen, he called "*Entamoeba coli*."

Nasse,¹ in 1891, described a case of ulceration of the abdominal wall following the drainage of an abscess of the liver. He failed to report confirmatory studies, but his case is credited as the first in the literature.

Menetrier and Touraine² in 1908 reported a second case of ulceration of the skin following drainage of an amebic abscess of the liver. Motile amebae were demonstrated in the exudate and lesion. Selenow³ in 1909 described four cases of pustular dermatitis of the head, neck and trunk from which he obtained organisms he identified as amebae. Other instances of amebiasis cutis following drainage of an abscess of the liver were reported by Basseres⁴ in 1910 and Carini⁵ in 1912, who described two cases. In 1912, Dagorn and Heymann⁶ and in 1916 Heymann and Ricou⁷ reported two more such cases. In 1919, Engman and Heithaus⁸ reported three cases of cutaneous ulcerations due to amebae. These authors were the first to use the term "amebiasis cutis."

In 1924, Runyan and Herrick⁹ reported one case following cecostomy and another following transthoracic drainage of an hepatic abscess. Kofoid, Boyers and Swezy¹⁰ in 1924 reported amebic ulcerations about the sinus of a draining abscess of the liver and on the limbs and trunk. Straub¹¹ in 1924 reported chronic ulceration of the glans penis following rectal coitus. amebae were demonstrated in the lesion. In

From the Regional Hospital, Fort Monmouth, New Jersey.

1925, Heimbürger¹² described an ulceration of the abdominal wall following spontaneous external rupture of an amebic abscess of the liver, amebae were found in the exudate and in biopsy sections of the skin. Van Hoof¹³ in 1926 described multiple ulcerations of the buttock in a woman with chronic dysentery, amebae were demonstrated in the ulcers. Tixier, Favre, Morenas and Petouraud¹⁴ in 1927 described a similar case of ulcerations in the perianal skin in which amebae were found. In 1928, Yorke and Adams¹⁵ reported amebic ulcerations following drainage of an hepatic abscess. Cole and Heidman¹⁶ in 1929 reported amebiasis cutis in an appendectomy wound. Marwits and van Steenis¹⁷ in 1929 reported an additional case following drainage of an appendiceal abscess, there was no preceding history of dysentery. The same authors¹⁷ in 1931 reported another case following rupture of a pericecal abscess in a patient who had had no previous dysentery and in whose stools no amebae could be found.

In 1931, Engman and Meleney¹⁸ reported one case of abdominal skin amebiasis following resection of the colon for amebic ulceration. Although amebae were demonstrated in the exudate and skin ulcer, the colon itself revealed healed lesions without amebae. The same authors reported another case following drainage of an hepatic abscess. Cheng¹⁹ in 1931 reported the same condition in a patient who also had kala-azar, and in 1932 Taylor and Hunter²⁰ reported a further case following drainage of an abdominal wall abscess.

In 1933, Kouri, Bolanos and Fuentes²¹ reported a case of severe ulceration of the skin in the pretibial region. After the patient's death, examination of the sections revealed amebae in the ulceration. In the same year, Botreau-Roussel and Huard²² reported one case of amebiasis cutis complicating the draining of an abscess of the liver and another following a colostomy in a patient with severe diarrhea.

Ngai and Frazier²³ in 1933, reviewed the reports of twenty-seven cases of this disease and presented three of their own. One was a patient who developed perianal ulcerations shortly after an episode of bloody diarrhea. The second was a Chinese woman who developed ulcerations about the vulva, anus and urethral orifice. Although she had evidence of lues and *Treponema pallidum* was demonstrated in the lesions, the ulcerations failed to respond to arsenical therapy. A biopsy revealed large numbers of amebae in the ulcerations. The third patient these authors reported developed a cauliflower tumor about the anus fourteen years after an attack of dysentery, the tumor was typical of a papilloma, but within the crypts there were amebic ulcerations.

In 1933, Crawford²⁴ reported amebiasis of the buttocks in a patient who gave no history of dysentery but who showed amebae in the stools. In 1935, Meleney and Meleney²⁵ reported a case of ulceration of the perianal region destroying the scrotum and the ischial region. Amebae were demonstrated by biopsy. In 1937, Hu²⁶ described perianal ulcers and fistulas and erosions of the female genitalia and ulcers

of the male urethra which were due to *Endamoeba histolytica*. In 1938 Manson-Bahr²⁷ described ulceration of the abdominal wall following a colostomy performed for what was believed at first to be carcinoma. *Endamoeba histolytica* were later demonstrated in the exudate from the ulcers, from the colostomy discharge and in the tissue sections of the lesions. In 1939, Fingerland²⁸ reported a similar case of ulceration following colostomy for sigmoid obstruction. In 1939, Shih, Wu and Lieu²⁹ reported a case of amebiasis of the penis.

Wyatt and Buchholz³⁰ in 1941 presented two cases with an excellent review of the literature, including a tabular summary of cases previously reported. Of their own cases, one followed drainage of an hepatic abscess and the other followed drainage of a tender mass in the left upper abdomen. In 1942, Jernstad and Launey³¹ reported a case of extensive ulceration of the abdominal wall following the drainage of an abscess of the liver. In another excellent review of the literature in 1942, Bacigalupo, Julien and Puga³ reported granulating lesions of the vulva in a virgin without previous diarrhea. Biopsy, exudate and culture revealed *Endamoeba histolytica*.

In 1942, Hermann and Berman²³ reported an additional case of ulcerations of the penis in a soldier with an exudate containing amebae. Amebae were also found in the stools.

Our own case report follows

A combat flier recently returned to the United States, was admitted to the Regional Hospital, Fort Monmouth, New Jersey on April 17, 1945 complaining of pain and bloody discharge from the anal region since January 1945.

Present Illness. In September 1944 this officer was shot down over enemy territory in China. On his way back to Allied lines he was assisted by Chinese guerrillas, eating native food and suffering an episode of bloody diarrhea lasting two weeks. The diarrhea subsided after he received oral medication and injections from a Chinese physician. Thereafter he had mild recurrences of diarrhea which he ascribed to the native food, and some soreness about the anus, which he ascribed to prolonged riding on the back of a mule. On January 24, 1945 he reached his base in India and on March 12 he arrived in the United States. During this period there was no diarrhea but he complained of persistent soreness and scanty bloody discharge from the anal region despite the use of ointments. He was transferred to the Regional Hospital with the diagnosis of pruritus ani, severe, which had failed to respond to symptomatic treatment. The exudate and stools had been examined, but no pathogenic organisms were found.

Physical examination revealed a husky young man walking with difficulty and complaining of severe perianal soreness. The skin about the anus for a radius of about 2 inches was composed of raw tender bleeding oozing granulations and irregular outlined ulcerations. Also, there was extensive maceration at the skin along the outer margin of the ulcerated areas (Fig. 73). In the right perineal region there was a similar area of granulations.

Laboratory Findings. Urine, complete blood count, Kahn, Frei test and chest film were normal. On the twelfth examination of the stools, a single motile ameba and several encysted forms characteristic of *E. histolytica* were seen. A biopsy specimen was taken from the border of a perianal ulceration. The section shows coagulated serous exudate along the surface of the epidermis. There is a moderate parakeratosis and acanthosis. On one end of the section there is an ulceration

which extends through from the surface of the epithelium deep into the dermis. In this area, there is extensive liquefaction necrosis with infiltrate consisting of polymorphonuclear cells and plasma cells. Along one edge of the ulcerated tissue there can be seen numerous amebae invading the necrotic tissue. Many of these organisms contain partly digested red blood cells in their cytoplasm" (See Fig 76)

Special Examinations Proctoscopy revealed an extremely hyperemic rectal mucosa which bled easily and presented numerous small ulcerations above the valves of Houston

Course There was no fever. The patient was put to bed with exposure of the lesions to air and frequent baths. The perineal lesion became rapidly worse and

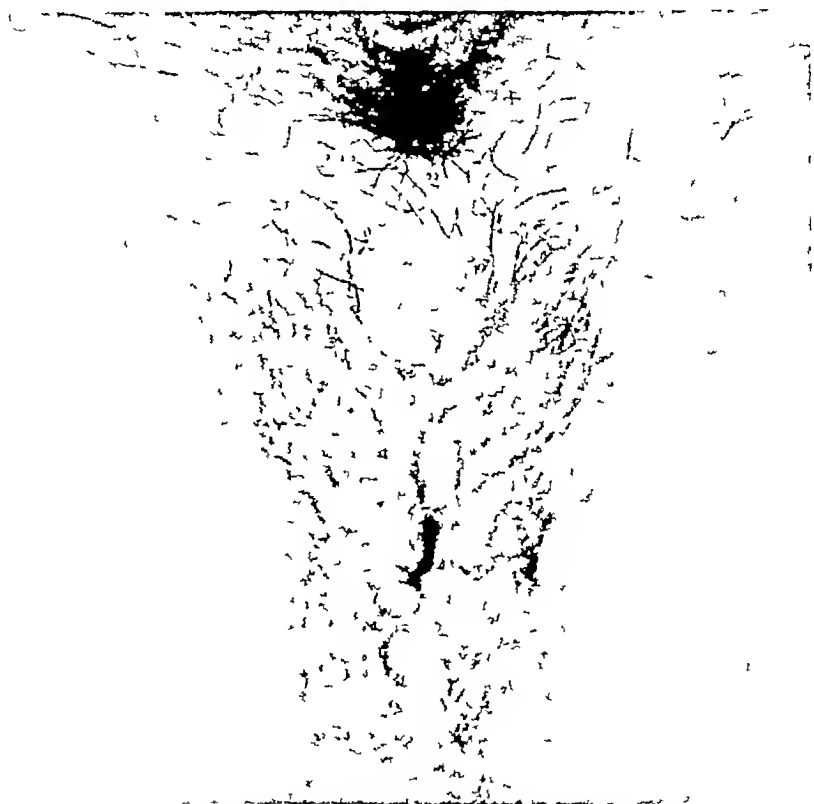


Fig 73—Ulcerating and granulating lesion in the perianal area prior to the administration of emetine hydrochloride

the ulceration extended into the deep fascia and muscles. A course of sulfadiazine led to no improvement. Following the discovery of the amebae, carbarsone was erroneously prescribed in the belief that the skin lesions were the result of the irritating rectal discharge rather than a true amebic invasion of the skin itself. While getting carbarsone, the patient developed a slight diarrhea and little or no change in the skin lesions. He was then started on a course of emetine, receiving 1 grain daily for ten days. Within two days after first receiving the drug, the diarrhea subsided and the perianal lesion was found to be granulating and slowly filling in from below. Within ten days healing was almost complete (Fig 74). After four days the perineal lesion also began to show healing. Forty days later the lesions had entirely healed (Fig 75). The perineal lesion left a hypertrophic

scar. The patient was given another course of carbarsone, no amebae were found in further examinations of the stools, a barium enema film of the colon was found to be normal and the patient was discharged without symptoms with instructions to be reexamined after six months and a year.

PATHOLOGY

The cutaneous lesions of amebiasis vary from granulomatous and ulcerative vegetations to deep ulcerations penetrating into the fascia

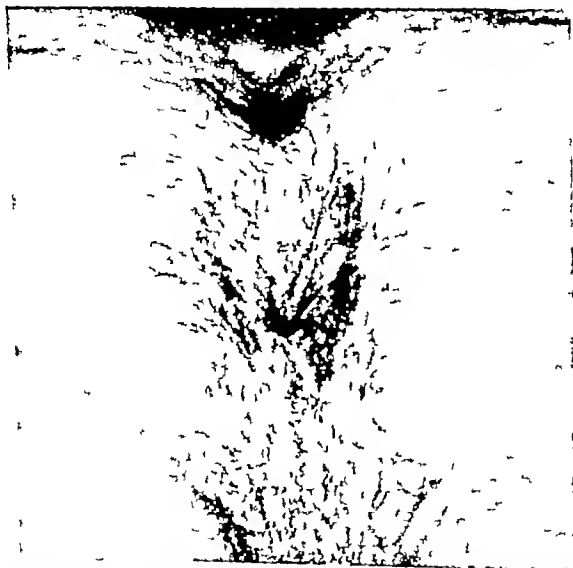


Fig 74—Clinical improvement and healing of the ulcerations ten days after administration of emetine hydrochloride was begun. Dusky erythema still remains.

and muscle. The characteristics have been best described by Engman and Meleney¹⁸ as follows

- 1 A rapidly spreading ulcerative process, the activity of which varies in different portions of the margin
- 2 A border which presents an irregular outline as a result of varying degrees of rapidity of progression of the disease process.
- 3 An overhanging edge of necrotic epidermis from which sanguinopurulent material may be expressed.
- 4 Advancing halo of erythema of different degrees which gradually changes from dusky red to merge with the normal skin color

- 5 The lesions are painful and tender on pressure
- 6 The floor of the ulcer is composed of indolent granulation tissue covered with debris and sanguinopurulent exudate

The majority of studies indicate that healthy skin cannot be invaded by the *Endamoeba histolytica*. It is generally necessary to have a pre-existing skin lesion, whether this be a surgical wound or a superficial erosion due to irritating discharges about the anus or genitalia (Bacigalupo, Julien and Puga³²). Once the amebae invade the skin, extensive

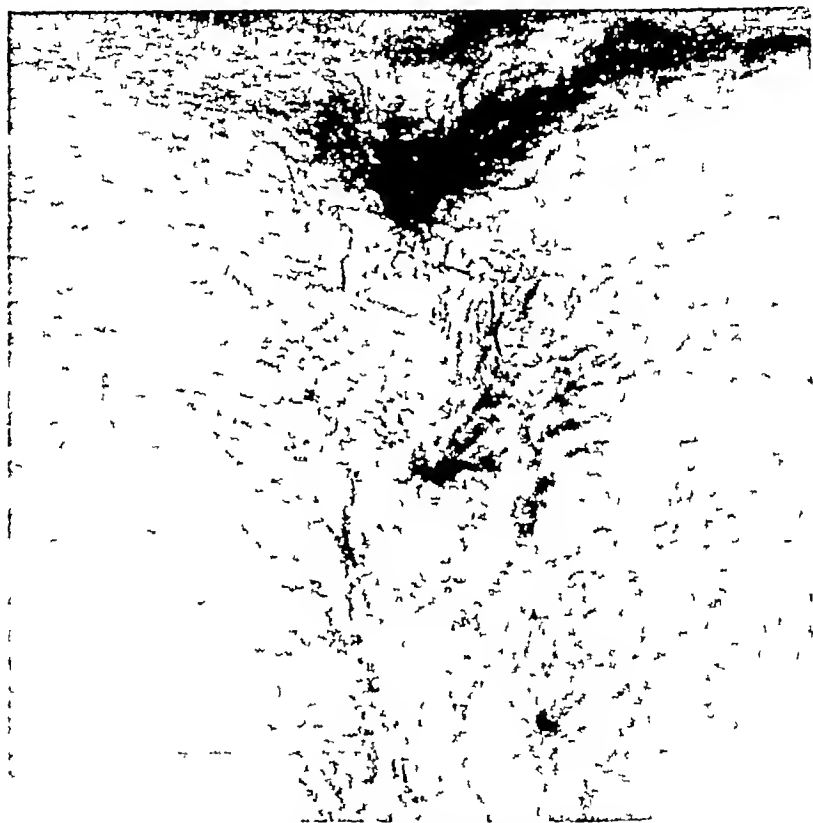


Fig 75—Perianal area completely healed three weeks after photograph in Figure 74 was taken

necrosis may follow rapidly owing to the proteolytic properties of the organism

Microscopic section reveals the epidermis to be hyperplastic in places and elsewhere completely destroyed. The corium is generally edematous and infiltrated by small round cells, plasma cells, monocytes and a number of polynuclear and eosinophilic leukocytes. The blood vessels are usually congested. In some cases, amebae have been found within the blood vessels and lymphatics (Heimberger¹²). Large numbers of amebae, often in clusters, may be found in the necrotic

areas, especially in tissue from the overhanging crater edge. The amebae are mostly round, varying in size from 20 to 40 microns in diameter, showing basophilic, vacuolated cytoplasm and containing red blood corpuscles. A central nucleolus, which is faintly eosinophilic, may be visible. After having reached the deeper layers of the epidermis, the amebae may be seen to have advanced between the epidermis and cutis, accounting for the tendency to form the overhanging edge.

Schaudinn believed that penetration of tissue by amebae was accomplished by pseudopodia penetrating mechanically between cells. The

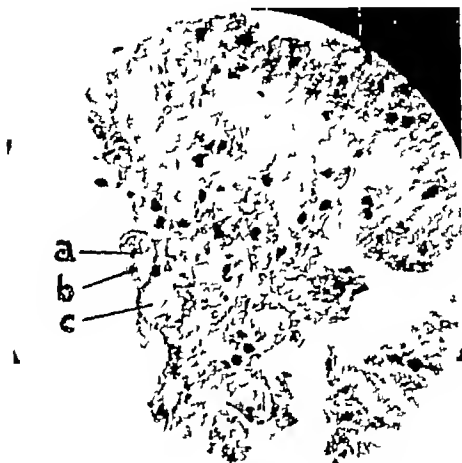


Fig 76.—Photomicrograph of ulcerated lesion ($\times 1000$). Amebae can be seen invading ulcerated tissue and cytolyxis is pronounced. (a, Nucleus b, partly digested red blood cells in cytoplasm of ameba c, granular cytoplasm of ameba)

opinion held by most pathologists at present is that amebae penetrate by means of their proteolytic secretion. Ngai and Frazier²³ observed amebae between fairly normal epithelial cells and concluded that Schaudinn's explanation may also be correct.

DIAGNOSIS

There are numerous lesions of the perianal region which may simulate amebiasis cutis. Among these are granuloma inguinale, lymphogranuloma venereum, ulcerative tuberculosis, mycotic infections, malignancies and ulcerative syphilids. On the abdominal wall a condition

to be differentiated is the postoperative synergistic gangrene described by Brewer and Meleney³⁴ In the latter lesion, the necrotic tissue is the result of an aerophilic nonhemolytic streptococcus growing in combination with *Staphylococcus aureus*

Amebiasis cutis should be suspected in every ulcerative or granulomatous lesion about the anus, in the genital region or on the abdominal wall A bloody exudate, rapid spread, the presence of amebiasis of the viscera, or the history of amebiasis should increase the suspicion It should be remembered, however, that the finding of amebiasis cutis may be the first indication of amebic infection elsewhere

To prove the diagnosis, the exudate should be examined and a biopsy specimen taken from the granulation tissue especially at the advancing edge of the lesion Amebae should be found in the exudate and biopsy specimen in order to confirm the diagnosis In addition, the patient must be investigated for the presence of an hepatic abscess and amebic colitis

TREATMENT

Once diagnosed, amebiasis cutis responds dramatically to *emetine* therapy This alkaloid derivative of ipecac was described in 1817 by Pelletier and first used in diarrheas by Bardsley in 1829 In 1912, Leonard Rogers demonstrated its effect in amebic hepatitis, amebic abscess and colitis (Goodman and Gilman³⁵) Emetine is the only amebicide known to be effective in extra-intestinal amebiasis

Emetine is available as the hydrochloride in hypodermic tablets It should be administered subcutaneously or intramuscularly in doses not to exceed 0.03 gm ($\frac{1}{2}$ grain) twice a day for not more than four to eight days³⁶ Toxic reactions consist of vomiting, diarrhea, abdominal pain, peripheral neuritis, acute nephritis, hemoptysis, myocardial damage, collapse and death The patient should be kept in bed and watched daily for these toxic effects preferably with an electrocardiogram before and during treatment Following subsidence of the lesions, surgical removal of necrotic tissue and skin grafting may be done if necessary Thereafter, the patient should be given periodic examinations and his stools searched for amebae because of the possibility of recurrences

SUMMARY

Amebiasis cutis is an uncommon but serious complication of amebic infection It has followed drainage of liver abscesses, appendectomies, colostomies and colitis, and in some cases has been the first evidence of the underlying condition Its detection is important because untreated it is a violent disease, treated, it responds rapidly to emetine An increased incidence should be expected in soldiers returning from areas of poor sanitation overseas It should be suspected in every case of ulcerating or granulating lesion of the abdominal wall or about the anus and genitalia

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POSTWAR ASPECTS OF THE TRENCH FOOT PROBLEM

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VETERANS with late sequelae of trench foot already are calling on civilian physicians for care. A treatment of the effects of exposure to cold has always been a military rather than a civilian medical problem, it would seem worthwhile at this time to summarize our present knowledge of this disorder. Emphasis will be placed on the residual aspects of the problem and my personal observation of 250 cases in the late stage.

Definition.—*Trench foot* is the term commonly applied to the effects of exposure of the feet to dampness and cold. It connotes the precipitating factors of cold, moisture, dependency, immobility and the constricting effect of shoes and clothing encountered in trench warfare.

Immersion foot has appeared as a syndrome in the present war and connotes immersion of the feet in cold water for long periods of time as in the case of the men shipwrecked in the North Atlantic. White¹ has shown that the pathology of this condition is due to the factor of cold and not merely immersion in sea water.

The term *frostbite* has been reserved by Lewis² for actual solidification of tissue from exposure to cold. Friedman³ at the Army Institute of Pathology believes that the distinction between "true frostbite" and injury produced by chilling without reaching the freezing point should be abandoned since the tissue reactions follow the same pattern.

The pathogenesis and morbid anatomy of trench foot have been described by Lewis⁴ as identical to those of *chilblain* or *erythrocyanosis* and by Blackwell⁵ as similar to those in immersion foot. Therefore the end result of exposure to cold is the same in trench foot, immersion foot and chilblain, the terms being descriptive of the precipitating factors involved. Frostbite is a result of more extreme exposure, probably enough to cause actual freezing of the tissue, and may be present in the superficial tissues in the severe cases of trench foot or immersion foot.

pacitated by frostbite in the winter campaign of 1941-42. No figures are available for our casualties during the present war but they were high during the campaigns of Attu, Italy (especially Anzio and Cassino) and on the Western Front between October, 1944 and January, 1945. For the week ending January 14, 1944, 46 per cent of all casualties in the Fifth Army were the result of trench foot.⁸

PRECIPITATING FACTORS AND MECHANISM

Trench foot is the result of a combination of factors. Its severity depends upon the duration of exposure, the degree of cold and varies inversely with the ability of footwear to keep the feet warm and dry. Contributory factors include dependency, immobility and constriction of the clothing and shoes which reduced peripheral circulation, body cooling from inadequate or wet clothing which results in loss of body heat and produces general vasoconstriction with circulatory stagnation, trauma of walking on damaged feet, dehydration, nutritional and vitamin deficiency.

The extremities of the limbs, especially the digits, cool faster and to a greater degree than any other part of the body. Immobility causes the loss of warmth usually obtained by the feet from the friction of walking and the increased blood flow of working muscles. Dampness of the feet brings the skin temperature near to that of the environment rapidly, much quicker than on exposure to air. The capacity of the skin to withstand solidification at -5° to -10° C, even at times to -20° C, has been called a supercooling effect by Lewis.² This property is lost when the feet become wet.

The first exposure to cold causes vasoconstriction which takes place in three separate reactions (Lewis).⁹ First there is a persistent local constriction of the superficial vessels as a direct response to cold. Next there is a transient immediate generalized vasoconstriction by reflex action through the central nervous system. Finally, the cold venous blood returning from the cooled skin stimulates the central nervous mechanism which is sensitive to cold and produces persistent generalized vasoconstriction. Closing down of the limb vessels, while safeguarding an excessive fall in body temperature, sacrifices a decrease in limb temperature to 10° C (50° F) or lower. This produces numbness, weakness of muscles, interference with proprioception mechanisms and fine control of movement.

The resultant ischemia causes anoxia of capillaries, increased capillary permeability, exudation and edema. Further damage is caused by trauma incurred from walking on damaged feet. In severe cases there may be formation of ice crystals in the cells of the superficial tissue.

Thawing is the period of greatest danger to the tissues. There is an intense inflammatory hyperemia due to injury to the cells by formation of ice crystals which on thawing release the so-called "H" substance (Lewis).² The hyperemia is also probably due to ischemic vessel dam-

age and to nerve injury causing vasomotor paralysis. This phase is accompanied by itching.

These factors cause vasodilatation with capillary permeability and transudation of fluids with resultant redness, swelling and heat of the part. At this point the pathologic picture is one of subacute inflammation. Involvement of peripheral nerves is suggested by the symptoms of paresthesia, hypesthesia, anesthesia and sudomotor disturbances.

PATHOLOGY

The pathology of the disorders arising from exposure to cold may be conveniently divided into the prehyperemic or ischemic stage, the hyperemic or inflammatory stage, and the posthyperemic stage.

Prehyperemic Stage—For the pathologic picture of the ischemic stage we must rely mostly on the rabbit experiments of Smith, Ritchie and Dawson.¹⁰ They exposed rabbits to the various factors favoring trench foot for two or three days, then made histological studies of the tissues.

Blood Vessels—Blood vessels showed no evidence of thrombosis. There was marked generalized constriction even of larger arteries. Swelling of the endothelial cells and vacuolation of the muscle fibers in the arterial walls were prominent. There was extravasation of fluid in the tissue spaces and, in some instances, vessel rupture and hemorrhage. Fibrin formation was found in the exudated fluid. There was perivascular infiltration of leukocytes and other phagocytes. Lewis² states that there is no interruption of blood flow in the mild cases but when necrosis develops it is brought on largely by injury to the vessels of the skin and adjacent tissues and that it is then the rule to find thrombi in the smaller arterioles and even larger arteries and veins.

Nerves—There was slight swelling of the axis cylinders but no degeneration.

Connective Tissue—These tissues showed fibrosis. Patchy acute degeneration of muscles (Zenker's hyaline necrosis) was reported by Blackwell⁵ in a case of immersion foot in a patient who died one half hour before rescue.

Hyperemic Stage—*Blood Vessels*—There was thrombosis only in areas where necrosis or infection was present. Excessive vasodilatation, diapedesis of red and white blood cells, and perivascular infiltration of inflammatory cells were noted.

Nerves—Ungley¹¹ found that histologically degeneration was seen in 90 per cent of nerve fibers of affected nerve trunks and that clinically there was evidence of degeneration and regeneration of fibers conveying motor, sensory and sudomotor impulses. Accompanying vascular phenomena suggested that vasoconstrictor fibers also were involved.

Muscles—In addition to fibrosis there was an effect of prolonged denervation. Long delay in regeneration of nerves seemed to cause degenerative changes in the motor end plates and muscle fibers and

impeded anatomical and functional recovery (Gutmann and Young, 1943)

Posthyperemic State—Blood Vessels—These appeared normal except for areas of gangrene or infection

Nerves—Ungley,¹¹ in his report on eighty cases of biopsy of interdigital nerves, two and one half to four months after development of immersion foot, and amputation specimens taken four to eleven months after immersion, found severe degeneration and early regeneration of the main nerve trunks and almost complete wallerian degeneration of the interdigital nerves

Severe degeneration has been found to occur with less prolonged ischemia than was needed to produce gangrene. Nerve regeneration occurred and denervated muscles returned to normal provided the ischemia was not so long as to produce irreversible degeneration and fibrosis. Blackwell⁵ found degeneration of myelinated fibers up to the knee in severe cases and endoneural fibrosis. These findings were most apparent peripherally. Goldstone and Corbett¹² noted the striking resemblance of immersion foot to peripheral neuritis.

Partial re-ervation of vessels may be responsible for the cold sensitive state and the development of Raynaud's phenomenon in this stage.

Muscles—Studies of surgical specimens and autopsy material by the Army Institute of Pathology³ revealed lesions of simple atrophy and ischemic changes comparable to those of Volkmann's contracture. Bone necrosis gave a picture similar to Sudeck's atrophy. They concluded that most of the damage was a consequence of disturbance in circulation and resultant vascular obstruction.

SIGNS AND SYMPTOMS

Prehyperemic Stage¹³—The first symptoms are a sensation of coldness followed by numbness. There may be temporary tingling and a mild aching or cramping pain about the arches, ankles and soles. Usually there is little discomfort in this stage. The patients complain of ataxia and a feeling as though they are "walking on blocks of wood". Swelling is mild to moderate and frequently not noted until the shoes are removed. The feet then suddenly become so swollen that the shoes cannot be put back on and the patients have to be evacuated. The skin is at first red and later becomes pale, mottled blue or purple. The feet are cold and anesthetic to pain, touch and temperature. Peripheral pulses are usually diminished and frequently absent. As the feet grow warm, swelling increases rapidly and a severe burning pain begins marking the onset of the second stage.

Hyperemic Stage¹³—This stage may last a few days to several weeks. Swelling increases rapidly and the feet become red, hyperemic, dry and hot. Peripheral pulses are full and bounding. Damage is greatest in the toes, distal part of the dorsum of the feet and in the balls of the

feet These parts remain edematous, hot and assume a livid cadaveric appearance. Blebs appear except in very mild cases and patchy areas of ecchymosis are common Superimposed damage to the peripheral vessels is suggested by ulceration and actual gangrene, usually of the toes. Although the appearance often suggests the necessity of amputation, in time there is demarkation and the gangrene is found to be superficial It sloughs off leaving healthy skin beneath Sensory disturbances in this stage consist of tense paresthesia described as intense burning pain which is relieved by cold and aggravated by warmth There may be stabbing, shooting pain from the ankle to the toes The periphery of the foot is usually anesthetic and thus merges proximally to areas of hyperesthesia and paresthesia Anhydrosis coincides with the sensory loss The edema usually begins to subside after four to six days and redness usually fades within a week to ten days The foot gradually assumes a normal color after exfoliation of superficial tissues In a few cases the feet become cold, blue and sweaty Complications are rare and include localized infection, cellulitis, lymphangitis, septicemia and phlebothrombosis

Posthyperemic Stage—This is the stage of this disease that may be seen by civilian physicians.

at rest, and then is proportionate to the amount of weight bearing sustained during that day. These patients frequently present muscular atrophy, limitation of motion of toes, pes planus, tenderness to pressure over the metatarsal heads and longitudinal arches, and have a peculiar foot deformity which has been described by Patterson and Anderson.¹⁶ It consists of hyperextension of the metatarsophalangeal joints and marked plantar flexion of the interphalangeal joints of the second, third, fourth and fifth toes, giving the appearance of a claw foot. The great toe is usually fairly fixed in mild plantar contraction. These deformities were considered by Patterson and Anderson as associated with pes cavus and reached greatest prominence during the fourth to sixth week. In the present series of cases the deformity of the toes was frequent but usually associated with pes planus. The deformity is due to atrophy of the intrinsic muscles of the foot. This distorts the intricate balance which is necessary for proper function of the foot and causes symptoms and strain at the calves, thighs and back.

White and Warren,¹⁷ in analyzing biopsy material of the posthyperemic stage, have demonstrated an increase in connective tissue and collagen involving blood vessels, muscles and nerves. The nerves are embedded in fibrous tissue and show endoneural fibrosis. They attribute the aching pain and the rigidity of toes to these factors. They state that the nerve pain tends to clear in six to eight months, the period in which collagen surrounding the nerves ceases to contract. In the present series of late cases these symptoms were present much later, up to twenty-two months.

X-ray films during the posthyperemic stage will frequently show demineralization of the bones of the feet. Where necrosis is present with loss of blood supply, the bones appear white and dense with little or no loss of calcium. No evidence of arthritic change has been recorded.

TREATMENT OF THE POSTHYPEREMIC STAGE *

Treatment of Discomfort on Weight Bearing—Many patients present muscular atrophy, fixation and limitation of motion of the toes, pes planus and arch tenderness. These changes have been described as similar to Volkmann's contracture and Sudeck's atrophy. The patient should be instructed to flex and extend his toes and foot and invert and evert the feet on a regular schedule of one-half hour three to four times a day. These exercises are usually combined with Buerger-Allen exercises which are believed to stimulate circulation. Buerger-Allen exercises consist of elevation of the legs at 35 to 45 degrees for two minutes, hanging the extremities over the side of the bed for three

* It is not within the scope of this paper to outline the prophylaxis or treatment of the early stages of this disorder. An excellent summary of this phase of care may be found in *The Bulletin of the United States Army Medical Department*, September, 1945.

minutes and then assuming the supine position with legs horizontal for three minutes. If there is limitation of motion of the toes, the patient should passively exercise them until the normal range is achieved. As the patient progresses, his exercises may be increased to trying to pick up a towel or marble with his toes. Pedaling a bicycle is excellent exercise for those patients who are well along toward recovery. The patient should be given walking instructions if he tends to favor his toes. Arch support has rarely given symptomatic relief but should be tried in the presence of pes planus. The patient should be encouraged to stay off his feet as much as possible until the atrophied muscles have been strengthened. Physiotherapy in the form of massage, active and passive exercise should be used. Whirlpool baths tend to soften the epidermis and are therefore poorly tolerated.

Treatment of Sensitivity to Cold—The presentation of symptoms of pain, aching, coldness, pallor or blueness of the feet, particularly the acral portions, suggests the presence of Raynaud's phenomena. "Test" lumbar sympathetic blocks should be performed and if effective, and if the symptoms have been present for months or years, sympathectomy should be considered. Actually the cases which have had unilateral sympathectomy during the early stages present identical complaints in both feet except for absence of sweating on the operated side.

Treatment of Sensitivity to Heat—Excessive sweating is difficult to control. The patient should be instructed to change his socks frequently enough to keep his feet dry. The feet should be washed with soap and water, rinsed and dried at each change of socks, three to four times a day if necessary. At the same time gentle massage with 70 per cent alcohol will help toughen the thin epidermis and application of foot powder as a drying agent will be helpful.

Treatment of Neurosis—A great deal of pain complained of by these patients is probably due to nerve degeneration and contraction of collagen around the nerves. Sympathetic blocks may be effective in relief of intractable pain but this procedure has been disappointing. Vitamin B₁ therapy should be utilized. Intraneural block is advocated by Barsky.¹⁸

Treatment of Circulatory Symptoms—Circulatory changes are very uncommon at this stage except for Raynaud's phenomena. If arterial insufficiency is present, manifested by coldness, pallor on elevation, diminished pulsation and oscillometric readings, the patient should be tested with a sympathetic block. If effective, sympathectomy may be considered. Buerger-Allen exercises should be utilized. The intravenous injection of typhoid antigen has been used effectively in the present series in cases presenting definite signs of arterial insufficiency. The flagellated H' antigen is best. The initial dose is one million killed organisms and subsequent injections every three days are gradually increased within the patient's tolerance for a course of ten to

twelve injections Flushing, warmth and throbbing of the feet can be attained without chills or a rise in temperature of over 100° F Codeine and aspirin should be prescribed for the side effects of headache and body ache The patient should always be warned to expect fever and chills, headache and body ache, to record his temperature and to watch for flushing, warmth and throbbing of the feet

Treatment of Infection—Hyperhidrosis is common and usually amenable to the local application of a 1 per cent aqueous solution of sodium hexametaphosphate applied twice a day

Epidermophytosis may be treated by potassium permanganate soaks (1:10,000) or one-quarter strength Whitfield's ointment twice daily In general, it is inadvisable to use strong solutions

Secondary infection should receive prompt care with bed rest, sulfadiazine or penicillin

Prophylaxis against Recurrence—Damage due to exposure to cold tends to cause permanent susceptibility to cold and recurrence of the prehyperemic and hyperemic stages is common If practical, the patient should live in a warm, dry climate If this is not possible the patient should be instructed on the following prophylaxis on exposure to cold

Animal oils such as lanolin tend to retain the supercooling effect of the tissues and should be applied in a thin layer to the toes and soles. Several pairs of socks afford more protection than one if the shoes are large enough to accommodate them without constriction Shoes should be waterproof When the feet get wet the shoes and socks must be changed at once

SUMMARY

A large number of veterans suffering from the effects of exposure to cold are already calling on civilian physicians for care

A summary of the present concept of the mechanism, pathology, signs and symptoms of disorders due to exposure to cold has been presented

A summary of the pathological findings has been given which tends to show that the signs and symptoms of the late stage of this disorder are due to nerve degeneration and regeneration and muscle atrophy and fibrosis, rather than to damage of the blood vessels In the late stage, vascular thromboses seem to be limited to areas of gangrene or infarction

Emphasis has been placed on the signs, symptoms and treatment of the posthyperemic stage, the stage which will be seen by the civilian physician Material for this was drawn from 250 cases not previously reported in the literature

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RUPTURE OF THE INTERVERTEBRAL DISK

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ONE of the most common single causes for hospitalization in Army general hospitals has been rupture of the intervertebral disk. Early in World War II 75 per cent of those patients with ruptured disks who were subjected to surgery were returned to duty as compared to 25 per cent of those who did not have surgery. As time went on, however, it was found that of those who were returned to duty, the majority were unable to complete a full day's work of military life, a finding which is quite comparable to the compensation cases of industrial life. Several methods of trial were used by the Army in an attempt to rehabilitate these patients and salvage them for some type of military service. Finally, however, it became evident that for the greatest efficiency of military manpower, patients having a definite diagnosis of ruptured intervertebral disk should be separated from the service (Surgery, if desired, is available before discharge in certain Army general hospitals for those having intractable pain.)

The above conclusion based on the assessment of the composite results from conservative and radical treatment is, in the eyes of the patient and many practitioners, a serious indictment on present day management of this condition. In view of this, some explanations for the end results and ultimate prognosis from surgery are indicated. Physicians having patients with this ailment under their care should be mindful of the fundamental nature of the disease and should explain this to their patients to avoid disillusionment or false hope on their part. Herniation of the nucleus pulposus depends on a rupture of the annulus fibrosus and is only a part of the picture of localized traumatic arthritis which must necessarily be present. This portion of the disk is now a foreign body lying partly within the spinal canal and partly within the intervertebral joint which has permanently lost its physiological integrity. Its removal should result in practically complete disappearance of the sciatica. If the sciatic pain is not relieved by the removal of the typically herniated disk, surgery has been inadequate and repeat surgery is usually indicated. Because these patients are relieved of pain following surgery, it should not bring one to presume that they are immediately cured. The back pain is commonly unaltered since the traumatic arthritis persists and must heal through the same process as any other arthritis by granulation tissue and fibrosis. The high percentage of cures in many reported series is often open to criticism when these patients are reviewed after return to strenuous activity.

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The wide variations from the typical ruptured intervertebral disk syndrome seen among patients referred as disk suspects blend from the classical picture to pictures of an entirely different disease entity. Over 1125 cases of low back pain and sciatica have been seen in military personnel at this neurosurgical center. From these, it has been noted that although ruptured intervertebral disks may be found in instances which are very atypical, the further from the typical syndrome the picture lies, the more rarely a ruptured intervertebral disk occurs. Because of this, cases may frequently have an interlaminar exploration which do not have a herniation of a nucleus pulposus and these cases are rarely improved by surgery whether a negative exploration be performed or a suspicious disk be removed. Occasionally in such instances a patient may have increased complaints. In view of this the importance of an accurate diagnosis and of care in the selection of patients for surgery cannot be overemphasized.

DIAGNOSIS

Characteristically, a patient with a herniated nucleus pulposus gives a history of low back pain and sciatica. These symptoms result from the pressure of the extruded nucleus on the fifth lumbar nerve root in the case of a disk between the fourth and fifth lumbar vertebrae or the first sacral nerve root in herniations at the lumbosacral interspace. Rarely a herniation occurs between the third and fourth lumbar vertebrae or at higher levels.

A routine history and physical examination should be supplemented by a special examination directed to the back and legs. Inquiry about the sciatica and low back pain should determine if it is intermittent, aggravated by coughing, sneezing, or straining at stool, and if it is relieved by bed rest. If numbness, paresthesias or subjective weakness occur in appropriate areas, the suspect becomes more typical. Special examination should include the following tests which reveal the effects of increased instability of the spine or those resulting from an increase in the pressure exerted on the nerve root by the ruptured disk.

Examination of the Back—The lumbar curve is usually flattened with a tilt to the pelvis usually listing away from the side of the sciatica. Motions of the spine are restricted in all directions. Hyperextension with lateral flexion toward the painful side is restricted, painful and if forcibly maintained for a few seconds may reproduce the entire pattern of leg pain. Percussion tenderness over the lower lumbar spine with radiation into the buttock or leg has been felt by some to be pathognomonic of a herniation of a nucleus pulposus.

Examination of the Leg—Straight leg raising test. With the patient lying supine the outstretched leg is passively raised from the table. There is always a check with production of pain on the affected side before the leg can be raised to 90 degrees. If the leg be forcibly elevated beyond the angle of check and held for a few seconds, paresthesias

will usually occur over the distribution of the affected root. This has been found to be one of the most valuable signs for localizing the site of the lesion in our experience.

Motor changes include weakness of dorsiflexion and eversion of the foot in lesions involving the fifth lumbar root, while weakness in plantar flexion points to a disk at the lumbosacral level. Some atrophy of the calf on the affected side is not uncommon.

In the *sensory examination*, nerve root patterns are notoriously inconstant and effort should not be spent in examining disputed areas between the fifth lumbar and first sacral nerve root distribution. Grossly, pain or paresthesias of the dorsum of the foot and great toe indicate involvement of the fifth lumbar root while the first sacral root is referred to the lateral part of the foot and fifth toe. For practical purposes it is safer to test the autonomous zones, the dorsum of the great toe for the fifth lumbar and the fifth toe for first sacral nerve root involvement.

Reflex changes—Diminution of the ankle jerk on the affected side usually occurs in a herniation of the lumbosacral disk, but in only 25 per cent of herniations in the space above. If the reflex is absent, it is even more strongly suggestive of the former.

Jugular compression test should reproduce the pattern of pain experienced on coughing or straining and if positive is pathognomonic of an intraspinal lesion.

Careful *x ray studies* of the lumbosacral spine and pelvis are essential in every case having low back pain and sciatica. *Myelography* and *special laboratory studies* should be performed when indicated.

DIFFERENTIAL DIAGNOSIS

Theoretically, other disease entities should involve the root between its emergence from the dura of the cord and junction with the sacral plexus to produce the typical picture of a herniated nucleus pulposus. However, intraspinal lesions otherwise situated or conditions irritating the sciatic nerve or its contributing plexus can prove most confusing. The most common of these to be considered in differential diagnosis are:

- 1 *Neoplasm of the cord and spine*, either primary or metastatic. Six cases have occurred in this series, in one of which the tumor was a "red herring," all symptoms arising from a huge herniated disk. Night pain is common in these cases and is not commonly relieved by rest. Detailed neurological examination, x-ray changes in the spine and myelography aid in establishing a correct diagnosis.

- 2 *Congenital anomalies* associated with strain are confusing. These include spondylolisthesis, spina bifida and other bony lesions common to the lumbosacral joint. Since these are frequently associated with herniated nucleus pulposus, it is difficult to rule out the presence of the latter without a myelogram.

3 *Fractures of the spine and pelvis*, as in the above, may require that a concomitant herniated disk should be ruled out by myelography

4 *Infectious, traumatic or degenerative disease of the hip* may simulate a rupture of the intervertebral disk by irritation of part of the sciatic nerve in the region of the acetabulum (One such case in this series showed typical symptoms and displayed an absent ankle jerk and hypesthesia of the first sacral dermatome. The patient was considered for exploration until x-rays revealed severe disease of the hip.) Routine lumbosacral spine films are taken to show the hip joint in all patients suspected of harboring a ruptured disk

5 *Tuberculosis and low-grade osteomyelitis* are most difficult to differentiate from ruptured intervertebral disk in the early stages. If no x-ray changes have occurred, they are frequently explored by mistake

6 *Marie-Strumpell's arthritis* is readily diagnosed clinically from the rigid spine and diminished chest expansion. Two of three cases in this series were identified by the latter examination in the absence of any x-ray changes

7 *Acute low back strain* is difficult to diagnose directly and it is the category into which many of these patients fall when it is felt that the diagnosis of ruptured intervertebral disk can be ruled out. The pathology here is probably edema about the apophyseal joints following strain and there may be encroachment of a nerve root at its foramen. The pain is usually less severe and more transient than in the case of a herniated nucleus pulposus. If the pain should persist or become intermittent, even though the picture is atypical, myelography is indicated

MYELOGRAPHY

According to Spurling, 60 per cent of the cases of ruptured intervertebral disk can be diagnosed clinically. This has been borne out in the present series. The figure, however, will vary with the experience and ability of the examiner. Recently, because a definite diagnosis without operative proof has been required for a medical discharge, myelograms have been done in most of the ruptured intervertebral disk suspects unless a classical clinical picture was present.

Criticisms of myelography in the past have fallen under three headings

- 1 Those referable to its diagnostic value
 - (a) That it was unnecessary, not diagnostic and possibly misleading
- 2 Those based on the dangers consequent to lumbar puncture itself
 - (a) That the lumbar puncture needle might pierce the disk and even produce a herniation of the nucleus pulposus in another interspace
 - (b) That meningitis can result from introduction of a contaminated needle or agent into the spinal fluid

- (c) The discomforts to the patient of the test itself and the common postlumbar puncture headache.
- 3 Those based on the faults of the agents used in myelography
- (a) *Lipiodol* If allowed to remain it forms arachnoid adhesions and later leaves a telltale picture on the x ray films to which the patient and future clinicians will attribute all symptoms and signs that may arise. Attempts made to remove it are painful and often traumatic.
- (b) *Diodrast* This is irritative, painful and its removal is more prolonged.
- (c) *Air* Though not injurious, it is associated with severe headaches and is inferior as a diagnostic medium

Many of these criticisms are quite valid. However, those directed at its diagnostic value do not apply in the majority of cases where it becomes a necessary procedure to establish a correct diagnosis.

Criticisms referable to the dangers of lumbar puncture indicate a lack of proficiency in technic. In the hands of an inexperienced operator, myelography can be a strenuous and harmful ordeal, but when done by one accustomed to a proper technic it is a precise, painless and benign procedure which avoids failures in diagnosis and discomfort to the patient. It is not unusual for a capable operator and radiologist to do from ten to fifteen procedures in a half day session, the patients remaining ambulatory.

Criticisms directed at the untoward effects of the agents used can be largely disregarded with the advent of pantopaque which is relatively nonirritating, easily and almost always completely removed and any remaining globules have been shown to become absorbed over a period of time.

The *advantages* of myelography are that it not only reveals the presence or absence of a defect but the number, nature, location as to the interspace, position in the interspace and relative size. From this information one can make a more direct surgical approach and may even derive some ideas of prognosis.

TREATMENT

The immediate treatment in the acute attack is primarily *bed rest* on a firm mattress which is supported by a fracture board. Heat and posture frequently relieve severe spasm more than narcotics. A favorite position is to place the patient on the side opposite the sciatica with a supporting pillow to the back. The affected leg is then slightly flexed and abducted to a comfortable angle where it is supported by pillows. If the pain persists especially if accompanied by scoliosis from muscle spasm, bilateral leg traction for a few days may give relief.

Conservative treatment is advisable in the initial attack and may also be indicated in the recurrent attack if the interval is long the patient's occupation is sedentary or the attacks not severe.

Surgery is indicated if the first attack is not relieved by conservative

measures or if the first attack is accompanied by severe neurological deficit. It is indicated in recurrent attacks of incapacitating pain and may be indicated for economic reasons if the nature of the patient's occupation provokes recurrent attacks.

Some have questioned the value of surgery for this condition and it is hoped that the discussion of the following cases will shed some light on the lack of uniformity in the results from surgery seen in every clinic. The operation for the removal of ruptured intervertebral disk, originally proposed by Mixter and Barr for alleviation of this particular syndrome, has been simplified by Spurling, Love and others to become a procedure of minimum risk and producing little morbidity. In most of these patients relief is satisfactory and convalescence is uneventful if the patient is not subjected to early physical strain or if he follows a sedentary occupation. It is probably largely because of this reason that the postoperative result in officers in this war has been a little over 20 per cent better than that in the enlisted men. One should be reminded that removal of a herniated nucleus pulposus is the treatment for the sciatica and that a traumatic arthritis persists. The pathological processes which have occurred and the reparative stages through which the patient passes postoperatively should be understood. The manifestation of these things varies with the type and location of the disk and behavior of the patient. The more common variations and their management are illustrated by the following case reports.

The More Typical and Uncomplicated Case—This type of case has popularized the operation and is the surgeon's delight.

CASE I—A 29 year old private of only four months military service was admitted, complaining of pain in the left hip, radiating down the left leg, with only minimal low back pain. In civilian life the patient had been a clerical worker and in his daily routine was not subjected to heavy work. There was no antecedent history which could be related to his present complaint. The patient first noticed the insidious onset of the pain after an overnight bivouac during his basic training. The pain became progressively worse, his severe attacks requiring hypodermic analgesics.

On admission the pain extended from the mid-buttocks to the back of the heel with paresthesias in the left thigh, calf and lateral aspect of the foot and was aggravated by any motions which stretched the sciatic nerve and by coughing, sneezing or straining. Examination revealed considerable paravertebral muscle spasm, some scoliosis of the lumbar spine with a pelvic tilt to the left. There was percussion tenderness over the lumbosacral region with accentuation of pain on hyperextension and lateral bending to the right, but no gross motor weakness nor atrophy. Hypesthesia was found over the first sacral dermatome on the left, affecting the posterolateral calf, the lateral aspect of the foot and small toe. The ankle jerk on the left was absent, but the reflexes were otherwise normal. Straight leg raising was normal on the right, but there was a marked check with pain at 45 degrees on the left. The jugular compression test was negative.

Because it was a typical picture and sharply localized to the lumbosacral disk, this patient was operated upon without a myelogram. It was not necessary to remove any bone and the ligamentum flavum was not removed, but only reflected

laterally disclosing the first sacral nerve root to be displaced over a soft mass of herniated nucleus pulposus. This offending body was of moderate size only and was removed in one piece. The interspace was further evacuated through the rent in the annulus, from which the nucleus pulposus protruded, but very little further material was obtained.

The postoperative course was most satisfactory the patient being immediately relieved from pain the day of operation. He sat up on the third day after which time he had latrine privileges and eighteen days following operation was allowed to go home on a convalescent furlough. On return from furlough after thirty days, the patient had no complaints of back pain and had had no recurrence of the sciatica. He stated however, that he had a tired feeling across the upper buttocks on maintaining a position for a long time. Observation was continued for another month with muscle building exercises until the patient was discharged under existing Army regulations.

It is common experience that better postoperative results are seen in ruptures of lumbosacral disks than of those at the level of the fourth and fifth lumbar vertebrae. This may be due to the fact that the weight-bearing angle is less direct, and the supporting ligaments and musculature are more efficient near their broad sacral attachments. The ruptured lumbosacral disk is also usually smaller than that seen in the interspace above. A transient sciatica experienced when the patient first gets out of bed is not uncommon. This is likely due to pressure from the swollen annulus fibrosus or from clots extruding through the rent in the annulus causing pressure on the root when the patient first attains an upright position.

Incapacity from Postoperative Back Pain upon Removal of a Large Herniated Nucleus Pulposus.—The following case is illustrative of this group.

CASE II—A 23 year old staff sergeant of slight stature was a gunner on a B-24 Bomber and had suffered three back injuries. The first was in November 1943 when he was forced to bail out of a bomber receiving a flexion injury to his back and fracture of his right fibula when he landed. In June, 1944 he again injured his back when he was blown out of a ball turret by a flak explosion. The pain lasted this time in his back and left buttocks for five weeks. In January 1945 he fell from a bicycle while riding on snow and again injured his back. The pain still persisted to the time of operation. Coughing and sneezing aggravated the pain. He was unable to bend or lift without pain in the back.

On examination there was restricted mobility of the lumbar spine with some flattening of the lumbar curve. The pelvis was tilted towards the right and there was tenderness over the lumbosacral spine. There was pain on hyperextension with some limitation of lateral flexion, more marked to the left. The straight leg raising test revealed a marked check with pain on the left at 30 degrees. The left ankle jerk was diminished as compared to the right. There was hypesthesia over the lateral aspect of the left leg and dorsum of the foot. Myelography was performed, which revealed a large defect on the left in the lumbosacral region. There was an anomaly of the lumbosacral space showing either a sacralization of the fifth lumbar or lumbarization of the first sacral vertebra. Because of rudimentary twelfth ribs and clinical signs, it was felt that the interspace effected was the fourth and fifth lumbar with pressure on the fifth nerve root. Because of this the myelogram was most helpful in localizing the interspace for operation. At operation the ligamentum flavum was incised and retracted laterally and as

the nerve root was retracted medially, a large mass of fibrocartilage was immediately exposed, having herniated out into the neural canal. This was removed and was followed by a similar mass, nearly as large, which had partially protruded through the rent in the annulus. When this was removed, the interspace was further evacuated, and considerably more degenerated disk was recovered. This left a large cavity which showed considerable instability on motion of the vertebra just above it.

During the first postoperative week the patient complained of slight pains in his leg and his lower back. When he was allowed up on the twelfth postoperative day, he developed severe low back pain with marked scoliosis and flexion deformity of the lumbar spine and a marked pelvic tilt, with some of the pain radiating into the left leg. Because of this, he was placed on fracture boards with skin traction applied to both legs. In this position, the pain was much relieved. Skin traction was removed in one week when the scoliosis and pain had completely disappeared. After a few more days of bed rest, the patient was again allowed up and this time was free of back pain and had a normal lumbar contour. He was fitted with a low back support and sent home on convalescent furlough. On return from furlough there was still no sciatica or scoliosis, but there was persistent low back pain with easy fatigability in the back. The pain was aggravated on prolonged sitting or standing and by changes in weather.

Such postoperative pain arises from the spasm to the supporting musculature of the injured joint as would occur in any other type of arthritis. The nerves forming the afferent part of this reflex spasm have been demonstrated in the annulus by Roofe (1940). Back pain is more common when a larger portion of the disk has herniated and, as a rule, the herniation between the fourth and fifth lumbar vertebrae are larger than those of the lumbosacral joint. A large disk even though degenerated and partially extruded, permits some collapse of the interspace upon its removal. This must of necessity promote more mobility and instability to the joint with changes in pressure and new strains introduced to the supporting ligaments, muscles and apophyseal joints. Because of this, motion of the vertebrae or changes in pressure on the injured joint space produce pain postoperatively as well as preoperatively. It is evident that some type of adequate back support must be maintained and that the patient must refrain from kinds of exercise placing strain on that joint until satisfactory fibrous healing and stabilization of the joint has occurred. One can also understand the urgent need for developing the tone of the supporting muscles which aid in splinting this joint and that these exercises must be taken in a recumbent position where they will not throw strain on the site of the herniated disk. After the acute postoperative period, back pain of some degree may persist in some cases off and on for many months or even years, being subject to weather changes and the like as in other types of arthritis.

Long-standing Traumatic or Degenerative Lesions Which Show Collapse of the Interspace, Osteophytes and Other Arthritic Changes—These may be diagnosed as "arthritis" per se in distinction to a localized traumatic joint where the remnants of an old herniated disk may be the cause of the symptoms. These cases are occasionally denied surgery because

of the bony changes. This is unfortunate since they frequently show the most gratifying response to surgery. The following is an example of this group.

CASE III.—A 33 year old captain, who injured his lower back when skung in 1938, developed a hematoma over the sacral region which had to be evacuated. Since that time he had intermittent attacks of low back pain and in November, 1943, while doing heavy orthopedic work in an Army general hospital first developed sciatic pain in the left leg. This was intermittent and became progressively worse. In November 1944 he developed a spontaneous peroneal nerve palsy which was associated with sitting with legs crossed. This showed progressive improvement. Symptoms of low back pain and sciatica became persistent and progressively worse, however being aggravated on coughing and sneezing.

Examination on admission to the hospital revealed spasm of the paravertebral muscles with a list to the left, restriction of motion of the lumbar spine and check on straight leg raising on the left to 30 degrees. There was 1 inch atrophy of the thigh muscles and $\frac{1}{4}$ inch atrophy of the calf on the left side with weakness of the peroneal muscle group, hypesthesia over the distribution of the fifth lumbar root, and slightly diminished ankle jerk on the left. X rays revealed some narrowing of the fourth and fifth lumbar interspaces.

Operation was performed without a myelogram and exploration of the third, fourth and fifth lumbar interspaces on the left performed. The third and fifth were normal but at the fourth interspace the nerve root was flattened out and tightly compressed. Instead of a soft nucleus pulposus, however, there was a hard bony and cartilaginous ridge displacing the root. With the root retracted, this was removed and from the interspace which was opened by removing this portion of the annulus and scar tissue, several degenerated fragments of the disk were removed, the nerve root being well decompressed by the procedure.

The postoperative course was uneventful. The patient was up on the twelfth postoperative day. He became ambulatory without symptoms. He was allowed to go home on sick leave, where he developed his back musculature with light exercise, avoiding strain to the spine. Three months postoperatively he was very active, playing tennis and similar games and was returned to limited duty as a surgeon. Seven months postoperatively he continued to perform strenuous daily routine duties without symptoms.

In the chronic and healed stages, according to Oppenheim, "osteoarthritis of the spine" or osteophytes of the vertebral margins with thinning of the disk do not cause symptoms unless they protrude into the neural foramen. In several of these cases portions of old nucleus pulposus, partially calcified, have formed this protrusion.

In cases of this group, the joint which is the site of the herniation has gone far towards healing and at surgery, little or no nuclear material or fibrocartilage may be found. The surgery here is chiefly confined to decompression of the nerve root over a hypertrophic bony spur. This situation is more commonly seen in the cervical disk than in the lumbar, which may partly explain the common satisfaction from surgery in the neck for this condition.

Recurrent and Double Herniations.—*Recurrent herniation* of a nucleus pulposus was more common in the earlier stages of development of the operation, but has become very uncommon since the practice of radical evacuation of the interspace at the time of removal of the

herniated portion of the disk. The incidence at this time varies from only 3 to 6 per cent in different clinics. There is another group of *double herniations* which in one reported series has been found to be a most common occurrence, while in other series it has appeared to be most infrequent. In our group there have been four patients with herniations of the lumbar disk in which there has been associated herniation of a cervical disk clinically. Three of these have been verified by operation. Five others have had double herniations in the lumbar region, three of these having herniation at the fourth interspace on the opposite side from that at the fifth. The following case, although unusual in some respects, is an example of herniations of two intervertebral disks in the lumbar region.

CASE IV—A 28 year old corporal, who was a salesman in civilian life, first noticed pain in the lower back after going over an obstacle course in basic training. This improved with strapping and conservative treatment, but when lifting a garbage pail on detail, he had a recurrence of the back pain with radiation of the pain into the right leg. This persisted for several weeks and gradually improved. However, the patient was unable to do duty and was referred to a general hospital. Examination revealed some loss of the lumbar curve and restriction of hyperextension on bending to the right. There was tenderness of the lower lumbar spine. Straight leg raising showed a check at about 40 degrees on the right with severe pain. The ankle jerks and knee jerks were equal and there was some hypesthesia over the dorsum of the foot. The patient walked with a decided limp because of the severe pain and was largely confined to his bed. Pantopaque myelography was performed which revealed a defect between the fourth and fifth lumbar vertebrae on the right. At operation a moderate sized disk was removed from this interspace with uneventful convalescence. This patient was allowed out of bed in two weeks with marked relief of sciatica which disappeared over the ensuing week. The back pain was also improved. The back was supported by a low back brace, which the patient discarded in two weeks because of absence of pain. Following a thirty day furlough, he was placed in reconditioning classes and then sent to a convalescent hospital where he was given special muscle training exercises to his back, which he performed faithfully. He followed the prescribed course through four different classes of reconditioning finally arriving at a condition that satisfied himself and his instructors that he was ready for duty. On return to duty, he was able to perform his assignment without any pain or discomfort.

One day while moving two heavy barrack bags, he twisted to one side to drop them from his shoulder. He was immediately seized with pain in his low back radiating into his left leg, when previously it had been the right that was affected. He was ultimately returned to the same general hospital for study and treatment. It was felt at first that he had an unstable joint in the region of the previous operative site, which, upon being strained, could possibly have extruded some fibrocartilage remnants beneath the left lumbar root. On examination, however, the left ankle jerk was slightly diminished and hypesthesia was present over the lateral aspect of the foot. There was a marked check on straight leg raising with a slight limp and pelvic tilt. Myelography was performed, which revealed a filling defect at the lumbosacral interspace on the left. This was verified at operation and a large herniated nucleus pulposus was found, displacing both cord and root. This was removed as one large degenerated mass of fibrocartilage. The interspace was further evacuated.

The postoperative course was uneventful, with marked improvement in the

back pain and sciatica. However, even after two months of further observation with marked improvement of the leg pain, this patient still had some complaints of pain in the low back on prolonged sitting or standing. This was considerably relieved by an adequate back support and the patient was discharged under existing regulations.

The excellent return of function following the first operation was probably largely due to the carefully supervised development of the supporting muscles of the injured joint. The clinical and myelographic findings before the first operation show conclusively that the second lesion at the lumbosacral joint was not a concomitant rupture but a new and unrelated incident. This immediately provokes speculation as to the importance of predisposing factors in the etiology of this syndrome.

Those Cases in Which a Bony Fusion of the Lumbosacral Spine is Combined with the Removal of the Ruptured Intervertebral Disk—Which patient should fit into this group is a matter of considerable debate since some surgeons feel that spinal fusion is never necessary while others feel it should be done in all cases in which the disk has been removed. In this series the factors influencing the combined operation have been (1) congenital anomalies of the lumbosacral spine, (2) the nature of the patient's occupation, (3) the location and relative size of the herniated nucleus pulposus, (4) history and roentgen findings suggesting prolonged instability of the spine. A combination of two or more of these factors has usually been present in the cases in which fusion was done at this hospital.

In the following instance, the nature of the patient's occupation in civilian life required an early return to heavy manual labor. There was evidence of involvement of more than one interspace and there was also a long history of recurrent attacks with weakness in the lower back which suggested instability.

CASE V.—The patient was a 28 year old captain of a rifle company who in civilian life was engaged in the trucking business. Eight years before the present admission, while playing football, he sustained a back injury requiring bed rest for two weeks. The disability recurred about six months later following the lifting of a heavy weight and required three or four months for recovery. Three years before admission, while in basic training, he again suffered acute low back pain following lifting, not severe enough to require hospitalization. The present attack which was of four months duration came on during a military offensive, when he was knocked down by a shell concussion and subsequently fell down a bank. Following this latter injury he suffered severe leg pain, requiring evacuation by litter. This pain which was aggravated by coughing, sneezing or straining was relieved by bed rest during evacuation to the Zone of the Interior. The patient also noticed a numbness of the lateral aspect of the left foot and ankle, extending into the dorsum of the foot and toes.

Examination revealed a severe scoliosis with a list of the pelvis to the left and with marked spasm of the lumbar muscles and tenderness over the lumbosacral joint. Straight leg raising was limited to 75 degrees bilaterally with pain. There was marked diminution of the right knee jerk. Both ankle jerks were absent.

X-rays revealed some reduction of the interspace between the fourth and fifth lumbar vertebrae and possibly of the interspace below. There was hypesthesia over the lateral aspect of the right foot and the lateral portion of the sole of the right foot. Myelography was done and showed a defect on the right between the fourth and fifth lumbar vertebrae. In view of these findings, together with questionable joint changes at the lumbosacral articulation, and because of the long history of recurrent attacks and the nature of the patient's occupation, combined operation was advised.

At operation no loose nuclear material was found in the neural canal, but there was a sharp protrusion of the disk between the fourth and fifth lumbar vertebrae on the right. This proved to be a thin membrane of scar tissue, an attempt at spontaneous healing of the defect in the annulus fibrosus at this level. When this was opened, the degenerated disk extruded itself spontaneously into the spinal canal and was removed with ease. The interspace was evacuated completely and a modified Hibbs spinal fusion with internal fixation by means of a Wilson plate was performed. The postoperative course was satisfactory, the patient being asymptomatic after the first week. Spinal fusion was protected by a back brace for five months following surgery, following which the patient was placed on inactive status.

The advantages of the combined operation for the heavy laborer are evident. Although the period of acute postoperative convalescence is possibly prolonged, the healing period of the arthritic changes of the interspace is greatly shortened because of the bony fusion. Immobilization of the joint which has lost its integrity removes its identity as a joint and all symptoms of future arthritis are thereby controlled when this region is exposed to the heavy strains of manual labor. Since experience has shown that a return to full duty in military life or to heavy labor in civilian life is out of the question for most of these individuals for many months, it is probable that the combined procedure should be used more commonly than it is at present. It may well have been used in Case II where it was withheld because of the patient's small size.

COMMENT

The importance of *muscle tone*, both as a predisposing factor and as an all important aid in rehabilitation, cannot be overemphasized. Many patients give a history of onset of this syndrome following some previous illness requiring bed rest and loss of muscle tone. In the military forces the greatest incidence of ruptured disks occurred in basic training where men became exposed to the rigors of training before sufficient muscle endurance was developed. Conversely, although they frequently complain of backache and back strain, this disease was not common in well-trained troops under combat conditions and it is unusual to have the condition occur in well-trained athletes. In view of this a regimen of muscle-building exercises should be followed by every patient postoperatively as well as during remissions. The exercises should be directed chiefly to the trunk muscles but include also those to the hips and legs. Because of the nature of the disease they should be taken recumbent until all symptoms have disappeared.

There is frequent need for adequate *back support* during the healing process. Many inadequate braces have been tried by the patients with little or no benefit. A brace is useless unless it protects the involved joint. Braces which rest on or just over the upper ilium may restrict motion of many joints above the lesion. By so doing they even increase the motion of the involved joint which is not adequately splinted. The ideal support should fit down over the buttocks and restrict the motion of the two lowest joints of the spine.

Healing, in the case of ruptured intervertebral disk, typically occurs by a fibrous connective tissue replacement which follows upon the granulation tissue invasion into the operative site. The much desired spontaneous bony union is an unusual and extremely late occurrence. In the recent postoperative case or in older cases with persistent and severe back pain the diseased joint may be frequently insulted by too early and too ardent activity. The patient should be aware that months after removal of the disk for the sciatica, he still has a traumatic arthritis and will be susceptible to back symptoms as long as there is delayed healing and instability of the intervertebral joint.

SUMMARY

The large number of military personnel suffering from low back pain and sciatica who were admitted to an Army neurosurgical center has provided an unusual opportunity not only for examination and treatment in cases of ruptured intervertebral disk, but also in the evaluation of results. Most of the patients referred for this condition do not have a classical clinical picture. Myelography here has been necessary to establish a correct diagnosis. This procedure when properly performed is benign and has been found to lend itself safely to the large volume output of a busy clinic. Patients considered cured of this syndrome by surgery do not usually tolerate heavy labor or full military duty, but one who has received surgery has been found to be more productive and to have a better prognosis than if treated conservatively. Patients having incapacitating pain or severe neurological deficit in whom a diagnosis of ruptured intervertebral disk is established should be treated surgically. It should be remembered that while the sciatic pain produced by compression of the nerve root from a herniated disk is relieved by adequate surgery, the localized traumatic arthritis, which always accompanies a disk herniation persists and may give continued disability from low back pain.

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POSTDIPHTHERITIC PARALYSIS

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NEUROLOGICAL symptoms as complications of diphtheria occur with sufficient frequency to make them of clinical importance because of the peculiar type or involvement, the pathology, and the pathogenesis which is not yet fully understood

Incidence—It is generally stated that some form of neuritis develops in from 10 to 40 per cent of all cases of diphtheria. Kay and Livingston¹ stated that 45 per cent of 141 cases of cutaneous diphtheria studied in the CBI theater from the standpoint of myocardial damage revealed some form of neuritis. In Rolleston's² large series, it was shown that the number of cases of paralysis following diphtheria was in direct proportion to the amount of time elapsing between the onset of the diphtheritic infection and the administration of the antitoxin. Only 3.6 per cent of patients receiving antitoxin the first day of infection subsequently developed neurological symptoms. But when antitoxin was not given until the third day after onset of infection, 21.4 per cent developed paralysis, and when specific therapy was withheld until the sixth day, 27.1 per cent developed some form of neuritis. In malignant or hemorrhagic diphtheria, with or without treatment, neurological symptoms may reach 100 per cent. There have been frequent assertions denying the link between the severity of the pharyngeal angina in diphtheria and the degree of later paralysis. Among the cases under observation this was found to be true in one patient who suffered mild pharyngeal angina and mild elevation of temperature, and later developed a complete syndrome of polyneuritis.

Pathogenesis—It seems to be well established that the paralysis following a diphtheritic infection is due to the production of a neurotoxin by the diphtheria organism. This is evident by the absence of bacteria from nervous tissues affected, even in close proximity to the site of the bacterial nidus.³ Postulations of a lymphogenic toxicosis have been brought forward by Walshe.⁴ However, Feiner⁵ states that the nature of development and recovery from the paralysis and the presence of a predominating peripheral lesion makes the hypothesis that the central nervous system is attacked via the blood stream or by centripetal diffusion of the neurotoxin doubtful. Walshe,⁶ analyzing the mechanism of the diphtheritic paralysis as a result of a study of wounds infected by the diphtheria bacillus, divided the neuritis into three groups: (1) the local or regional, (2) the specific, and (3) the general. The local paralysis is well demonstrated by the early palatal,

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pharyngeal and laryngeal paresis believed due to involvement of the nerves in the region of the infection. The paralysis of the ciliary muscle is called specific because it is peculiar to diphtheria and may occur in the absence of general paralysis. Finally, generalized paralysis or polyneuritis occurs and is probably due to the presence of the neurotoxin in the blood stream. However, the exact method is not clear as indicated above.

Time between Initial Infection and Onset of Palsies—The period of time elapsing between the initial acute diphtheritic infection and the onset of the various palsies is quite uniform in most instances. The palatal paresis usually appears first and although it may be the only involvement, it is usually followed quickly by pharyngeal and laryngeal paresis. This usually occurs between the second and third week after the initial onset of illness, but may be sooner or later. It is felt that the later the paralysis appears the less likelihood is there of a widespread paralysis. The ocular palsies usually appear between the third and fourth week involving predominately the muscles of accommodation and less often the extraocular muscles. Shaw⁷ reports observations made at Guy's Hospital, London, that the ocular palsies are felt to be an indication of individual sensitivity to the diphtheria toxin and that ciliary and extraocular muscle paresis may occur whether antitoxin has or has not been administered. Further observations indicated that usually full return of function is to be expected and that no drug influences these palsies. There may or may not be sphincter involvement. The general paralysis usually begins after the fourth week.

Diagnosis—In most cases of general paralysis that have not been preceded by a positive diphtheritic infection and cranial nerve involvement as in the local and specific palsies described, it is impossible to differentiate the neurological picture from the diffuse polyneuritis classified under Guillain-Barré syndrome. The differential criteria used to make a positive diagnosis of postdiphtheritic polyneuritis were as follows: (1) history of pharyngeal angina and demonstration of virulent diphtheria organisms, or (2) the history of pharyngeal angina followed by palatal, pharyngeal and ciliary muscle paresis. In cases without ciliary muscle paresis the diagnosis was considered doubtful unless virulent diphtheria organisms had been or were demonstrable, even though a history of pharyngeal angina was present.

Pathology—The neurological findings in the general polyneuritis are well known and will not be elaborated upon. It is worthy of note, however, that the distal muscle groups were usually more severely involved than the proximal and the sensory disturbance followed essentially the same distribution. Respiratory paralysis due to involvement of the intercostal and phrenic nerves is an extremely serious complicating factor. Of six cases observed by Blackwell⁸ with diaphragmatic paralysis as well as palatal and pharyngeal paresis treated in

a respirator, there were two recoveries and four deaths. The respirator was considered life saving in one case observed by Arena and Rasmussen.⁹

The clinical pathological findings are fairly uniform. The diphtheria bacillus is never found in the tissues involved. The cerebrospinal fluid findings are the most interesting and always reveal an excess of total protein. However, Arena and Rasmussen⁹ reported normal spinal fluids in four of nine children under observation with postdiphtheritic neuritis. Occasionally there is a rise in the spinal fluid cell count and glucose in the early stages of the polyneuritis. Cultures of the nasal and pharyngeal mucosa may reveal virulent diphtheria organisms several months after the acute infection.

Treatment—Treatment is directed toward general supportive measures. Nutrition must be considered during the period of palatal and pharyngeal involvement as the patient usually is unable to take fluids or solid foods without regurgitation. Inhalation of food must be guarded against as in some cases where there is respiratory paresis the ability of the patient to expectorate such material would be greatly reduced. There is usually marked atrophy of the involved muscle groups. Extensive physiotherapy must be carried out to preserve all affected muscles. The use of the respirator must be instituted immediately upon evidence of respiratory paralysis. Painful joints, especially the feet, may be present as the patient resumes the ambulatory state. Proper supports should be utilized to alleviate the pain as much as possible. Once the patient has noted some evidence of improvement, progress usually is fairly rapid.

ANALYSIS OF SEVENTEEN CASES

There is no doubt that there were many cases of neuritis following diphtheritic infections in all theaters of war in which the patients recovered and were returned to duty. The observations included in this report are based on seventeen cases of polyneuritis of diphtheritic origin which were sufficiently disabling to warrant evacuation of the patients to the United States.

Three of the seventeen cases under observation were cutaneous and fourteen were faucial diphtheria. In only two of the seventeen cases was diphtheria diagnosed and proved by culture at the onset of pharyngeal angina and followed by treatment with adequate quantities of diphtheria antitoxin. One case of cutaneous and one of faucial diphtheria, not previously proved by culture, revealed virulent diphtheria organisms obtained from the nasal mucosa four and three months respectively after onset of the initial infection. The onset of the neurological symptoms varied from three to eight weeks after the initial infection. The onset of symptoms did not always follow the pattern of local, specific and generalized neurological involvement. The spinal fluid findings were similar in all seventeen cases, however, spinal

fluid examination was done on only eight of the seventeen cases at the time of greatest neurological involvement. The finding of an elevated total protein and normal cell count was present in all eight cases and these readings varied from 108 mg to 277 mg per 100 cc of fluid. As the neurological symptoms diminished, the spinal fluid total protein diminished accordingly and in all cases but two had returned to normal at the time of discharge. Three cases revealed abnormal electrocardiograms during the early stages of the disease but were normal at the time of discharge. The main residual complaint, after clinical recovery was manifest, was chronic fatigue and lack of physical endurance. This complaint persisted only in the most severe cases. One patient developed a moderate amount of osteoporosis of the tarsal bones of both feet, giving him a great amount of pain as he attempted to resume the ambulatory state.

REPORT OF CASES

Four cases are briefly summarized to indicate the different types of cases under observation.

Case I Paralysis Following Faucial Diphtheria Diagnosed and Treated with Adequate Antitoxin

This 24 year old soldier developed acute sore throat December 8, 1944 in Italy and was hospitalized and treated with 140,000 units of diphtheria antitoxin within seventy-two hours. He recovered rapidly and was discharged to duty January 8, 1945. Approximately February 1, 1945, the patient noted progressive numbness and paresthesias of fingers and toes, followed by general paresis of the distal muscle groups of all extremities. A few days after the onset of the above symptoms, the patient noted blurring of vision for a period of approximately one week.

The patient was rehospitalized, and neurological examination revealed a general paresis most severe in the distal muscle groups of all four extremities, complete loss of all deep reflexes, loss of position and vibratory sense in the lower extremities and reduced in the upper extremities. A positive Romberg was noted. No cranial nerve involvement was demonstrable.

Spinal fluid examination on February 28, 1945 revealed 166 mg of total protein per 100 cc., and 7 white blood cells. A second and third spinal fluid examination done on March 8 and 16, 1945 revealed a total protein of 200 mg per 100 cc and 4 white blood cells at each examination. A final spinal fluid examination on August 7, 1945 revealed a total protein of 90 mg per 100 cc with no white blood cells. Gold sol curve and the Wassermann test were negative in all spinal fluid examinations. Electrocardiograms done during the acute phase of the disease and on dismissal were normal. At the time of the final spinal fluid examination the patient was clinically recovered and was discharged from the hospital.

Case II Paralysis Following Undiagnosed and Untreated Faucial Diphtheria in Which Virulent Diphtheria Organisms Were Obtained from the Nasal Mucosa Three Months after the Initial Infection

This 28 year old soldier had been a prisoner of war for ten months in North West Germany and was liberated January 31, 1945. There had been many cases

angina, he noted difficulty in swallowing and regurgitation. This progressed, and by June 4, 1945 he developed severe hoarseness. Also about June 4, 1945 he began noting blurred vision which was progressive for thirty days before any evidence of improvement was manifest. About June 15, 1945 the patient began noting paresthesias and numbness in both feet spreading proximally and associated with marked paresis of the distal muscle groups of the lower extremities. The upper extremities became involved in a similar manner the following week. There was mild paresis of the abdominal and intercostal muscles, but no definite evidence of diaphragmatic paresis. There was some anal sphincter paresis which lasted ten to fourteen days.

Improvement of the general polyneuritis began about August 1, 1945. Spinal fluid examination done for the first time August 7, 1945 revealed 220 mg of total protein per 100 cc., and no white blood cells. The gold sol curve and Wassermann test were normal. This was one of the most severe cases of polyneuritis and the rate of improvement has been much less rapid than in the average case. At the present time the patient is suffering considerable pain in both feet on attempting to walk, due to osteoporosis of the tarsal bones.

SUMMARY

All cases of postdiphtheritic polyneuritis under observation revealed similar spinal fluid findings, i.e., an elevation of total spinal fluid protein in proportion to the severity of the neurological involvement, and a normal spinal fluid cell count. One case revealed an abnormal gold sol curve during the early stages of the polyneuritis.

All cases did not demonstrate the three phases of neuritic involvement described in the literature. Criteria for making a differential diagnosis were described.

A significant feature of this form of polyneuritis is the fact that recovery is to be expected if respiratory paralysis is avoided during the early stages. Once evidence of improvement is manifest, recovery usually is rapid.

Four cases have been briefly summarized indicating the types of cases under observation.

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THE SIGNIFICANCE OF A PSYCHIATRIC DIAGNOSIS

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THE examination of millions of men during the war has forced increasing attention on an old problem—the *emotional factors in illness*. The early recognition of these factors and the proper psychiatric attitude cannot be overemphasized. The doctor who recognizes the psychogenic component of his patient's disturbances should be able to practice more efficiently, effectively and happily. He will be better prepared to meet new clinical developments, to understand the cause and course of disease, and to properly evaluate the prognosis.

Doctors have had good training in recognizing the organic features of illness, but have been inadequately educated in evaluating the psychologic aspects of disease. The problems on the wards of our general hospitals during the war made this lack of psychiatric knowledge evident to physicians. Most have evinced a sincere desire for help in understanding the emotional factors in their patients.

A case reported by Lipkin and Sharp clearly presents the necessity of being always alert for emotional components in a sick individual.

A young Negress, whose chief complaints were increasing weakness and a "pins and needles" sensation in her hands and feet, presented upon examination polyneuritis involving all four extremities, and marked enlargement of the liver. Her history revealed a meager food intake for many months preceding her admission. She related that four years ago she was admitted to Knickerbocker Hospital greatly emaciated, weighing 65 pounds and suffering from bilateral foot drop. She was treated with vitamin concentrates, liver and a high caloric diet and progressed rapidly to complete recovery. Within a few months she returned to her old dietary habits, and was readmitted to the Knickerbocker Hospital. Recovery was again rapid and complete. When she left the hospital she was warned as she had been upon her first discharge, that her symptoms would return if she failed to obey instructions concerning diet, and that her undesirable eating habits were jeopardizing her life. She understood the instructions clearly. She appreciated fully what the penalty would be if she disregarded them, and yet, about a year later she was admitted to the New York Postgraduate Hospital with these same complaints. Again she had failed to follow the instructions. Conversation with her made it obvious that she was quite intelligent and not at all lazy. Investigation of her background revealed that she was the youngest of a large family and was cared to and protected by her mother and older sister. The patient attributed the illness to the death of her mother. She was terribly depressed by it, and a month later attempted suicide. Her older sister assumed maternal responsibility. Six months after the death of the mother the older sister suddenly died. The separation from her mother and her mother's substitute was so violently resented that the patient reacted in a regressive manner and ate only when she was cared for and fed. After adequate psychiatric treatment her bad eating habits ceased and her symptoms did not return.

From the Tilton General Hospital, Fort Dix, New Jersey

As indicated in this case, the recognition of a neurosis is important. At the same time, to make a diagnosis of a neurosis when not present is of serious consequence. It is as serious as making an unconfirmed diagnosis of tuberculosis, syphilis or cancer. It may even be the cause of overlooking a correctible organic condition, as occurred in the following patient.

A 25 year old soldier was admitted to the hospital because of severe pain in his throat. The first examination did not reveal any evident pathologic changes. Because of his persistence in demanding relief from his pain, he was given placebos and sterile "hypos." Suspected of having a neurosis, he was sent to the psychiatrist for consultation. He was apprehensive and tense at the time of the interview. The psychiatrist found that the patient had a peritonsillar abscess which was not previously detected. Evacuation of the abscess cleared up the "neurosis."

CLASSIFICATION

No attempt will be made to classify specifically emotional factors in illness. The following outline will, however, suffice for practical purposes. The common manifestations of emotional disorders which are met in the daily practice of medicine can be grouped as follows.

The *first group* includes those individuals with organic diseases and secondary emotional disorders. It has long been recognized by physicians, often intuitively, that emotional factors affect the course of organic illness. It is reputed that John Hunter said, "My life is in the hands of any scoundrel who cares to arouse my ire." He had coronary disease and died in a fit of temper.

The *second group* is composed of those disorders with structural or physiological changes, such as hypertension, peptic ulcer and asthma, in which the psychogenic factors are responsible, at least in part, for the condition.

The *third group* comprises those patients with somatic complaints but without structural disease. These individuals form perhaps the largest group and include those with complaints referable to every system of the body. Some have disorders limited particularly to the gastrointestinal tract, others to the cardiorespiratory system, and still others to other systems. As a rule, more than one system is involved.

The *fourth group* is made up of those disorders with primarily psychic manifestations. These include anxiety states, conversion hysteria, reactive depression and obsessive-compulsive reactions.

An *anxiety state* is present when the patient has a feeling of tension for which he knows no cause—which is not associated with any particular thoughts or somatic complaint. The physician can see the evidence of tension in the patient's face, hands and general appearance.

Conversion hysteria most commonly appears as some disturbance in the sensory-motor apparatus. These reactions include paralysis, anesthesias, blindness, deafness and aphonia.

Reactive depression is a situational disorder usually out of propor-

tion to reality factors. The patient is in good contact with his environment, but is somewhat retarded. He has feeling of inferiority and self-blame.

Obsessive-compulsive reactions are the most severe in this group. Certain thoughts or ideas force themselves into the patient's consciousness or he may feel compelled to count, touch or perform ceremonials.

METHODS OF DETECTION

The means of detection of emotional disorders vary sufficiently from the methods used in general medicine to warrant elaboration.

1 *Listening*—One of the most difficult things to do is to listen to another person. Listening is an active process—not a passive one. The patient is keenly aware of true listening. One *gives* the patient something when one listens to him. Frequently, patients want to tell their whole story and indicate this by beginning a rather roundabout discussion immediately after mentioning their symptoms. The busy practitioner who does not recognize this misses an invaluable opportunity to help his patient. It is neither necessary nor possible to answer all the patient's questions for many of his problems have no answers. It is even dangerous to answer some questions. Psychotherapy takes place during the listening period. In addition a better evaluation of the patient is obtained during this period.

2 *History*—For proper psychiatric understanding, it is imperative to know the patient's background. The history is the most important single part of the examination. This is particularly true in psychiatry, for by means of the history, we learn the character-structure of the patient. In this regard, the family doctor is in an enviable position for he often has detailed historical knowledge of his patient. He usually knows the family, school adjustment, work record, home set-up, problems and often even the precipitating factors in a particular illness. The consulting psychiatrist is not so fortunate. He must spend a good deal of time learning all these facts, and in addition, determine the character make-up of the patient's parents and siblings. It is important for the physician to evaluate the patient's relationship to other members of the family. Was he emotionally dependent upon the family? Was there continuous strife? Did the parents quarrel? Did the home break up?

The following case record illustrates the importance of obtaining a good family history. It demonstrates the influence of a neurotic mother in the development of a neurosis.

A 39 year old unmarried male had numerous complaints, including headaches, "upset stomach," restlessness, "palpitations," pain behind the right ear and "nervousness." His mother was a partial invalid. For years she had severe "sick headaches" and frequently was confined to bed. In addition she had "stomach trouble," "fainting spells," and was considered temperamental and nervous. At the age of 13 the patient had left school to work on his mother's farm. He remained single

because he had "to take care of mom first." Lately, he says he has become "tight and jumpy," and when he becomes nervous, his heart "runs off." During the examination the patient was tense, apprehensive, uncomfortable and unhappy looking.

Personal History—In the patient's personal history, we are interested in knowing more than what illnesses, operations and accidents he has had. What techniques did he develop early in life to meet difficult situations? Was he "sickly"? Did his mother take him to the doctor frequently? Did the doctor say he had a "slight leakage of the heart"—tell him not to overexercise and give him a tonic? Was he frequently out of school because of "colds"? Did his diet have to be closely watched? Did he change jobs frequently because the work was too hard? Did he remain at one job at low salary when he was obviously fitted for a better position? Did he have girl friends? Is he married? Is the marriage successful?

Present Illness—The onset of the present illness is often difficult to determine. As a rule, the patient has had symptoms for years. The description the patient gives of his disorder is almost always bizarre, inconsistent, and does not fit the pattern of an organic syndrome. His complaints are multiple, frequently involving several systems. He may speak of "nervousness." Like all lay terms, it is as nonspecific as "rheumatism," yet it does tell us that the *patient is aware of emotional changes in himself*. He often assumes that the "nervousness" is secondary to a "headache" he has been having, whereas the reverse is true. In eliciting the present illness, the total life situation at that time must be determined, and if possible, the precipitating factors.

3 *Observation*—So much can be learned about a patient if we will only look at him. Observe the way he walks into the room and the way he takes a seat, his posture in the chair, and the position of his hands and legs, his activity while in the room, the movement of his eyes, and his facial expression. The latter may indicate apprehension, anxiety, fear, suspicion, apathy or depression.

In the course of the physical examination, more takes place than merely the physical study of the person involved. By his actions the patient indicates to the doctor a good deal about himself. The patient may be hesitant, flushed, perspiring freely, restless, jumpy, ill at ease, and may show special anxiety when particular parts of the body are exposed and examined. The alert doctor will observe all these things, and will add them to his store of data evaluating the patient. Conversely the doctor, by his actions, benefits or harms the patient. The following case is illustrative.

A white male, aged 32 years, an intelligent, sensitive individual, was rejected for Army service. He was told, "You have a serious leak in your heart, and should be under doctor's care all the time." At the age of 13 the patient had rheumatic fever. He read about rheumatic fever and knew about its possible sequelae. As a result of the doctor's comment, he developed heart consciousness.

precordial discomfort easy fatigability, insomnia loss of appetite and numerous other symptoms. After several months elapsed, he was examined by a competent cardiologist who recognized the emotional factors involved and reassured the patient that his murmur was of no clinical significance. The patient rapidly returned to his former level of efficient functioning and good health

Evaluation of Data—The evaluation of the accumulated data is not easy. Skill in accomplishing this comes only with practice and application. Before this can be accomplished, the limits of normal must be understood. "Normal" does not mean perfection. It means that type of make-up common to the greater number of people. The individual who is considered normal on physical examination does not have a perfect body. One can find many defects, such as acne vulgaris, epidermophytosis or pes planus, yet we say that individual is physically well. Similarly, an individual may have some deviations of his personality and be considered well. A certain degree of anxiety is appropriate in particular situations. All people who are tense or who cry or who become angry or upset do not have a neurosis. Neurosis is not a fleeting experience. It is rather a disorder which has definite structure, pattern and substance.

In the course of a psychiatric survey, one should determine not only disabilities, but also abilities. Just as one utilizes the well leg to splint the fractured one, so in psychiatric treatment one utilizes the assets of the patient to help carry and modify his liabilities.

The recognition of a neurosis and the diagnosis of such a disorder is not a negative accomplishment. It is not the equivalent of "there is nothing wrong with you, it's just your nerves." Instead, it represents a positive diagnosis of which the patient should be informed. Otherwise, the patient misunderstands and arrives at an erroneous and even harmful conclusion. Patients want a specific response. The patient wants to know what is wrong; that is, in what area he is not functioning correctly. The type of response that will be given to a patient will necessarily vary with the patient's intelligence, feelings and the severity of his disorder. It is not necessary to tell the patient he has an obsessive compulsive psychoneurosis due to anal erotic fixations as a result of faulty psychosexual development, any more than it is necessary to give the patient an elaborate discussion of the etiology and course of lymphosarcoma. The patient, however, should be told frankly and honestly what is wrong with him in language which he can understand.

Common Errors—Psychiatric diagnoses are very commonly made by exclusion. This is a medical error and an injustice to the patient. A psychiatric disorder is a positive quantity. It has been emphasized that as the fundamental concepts of psychiatry have become more familiar to a greater number of physicians, errors have increased rather than diminished. Many injustices are done, and incorrect diagnoses are made. Some of these can be avoided by leaving difficult problems un-

solved and continuing to search thoroughly for the cause, rather than vaguely attributing it to a psychogenic factor. In general medicine and surgery, we give nonspecific (supportive) treatment when we have no specific diagnosis or treatment available. Similarly, one can do the same for whatever psychogenic components are present. This, however, does not obviate the necessity for making an accurate psychiatric evaluation of every patient. Arriving at an organic diagnosis does not exclude the presence of a psychiatric disorder any more than arriving at a psychiatric diagnosis excludes the presence of an organic disorder, as both may coexist and both need attention. It is not an "either-or" decision, but rather the entire patient, his background, his present situation, his organic disorder and his psychologic and somatic reactions to the disability. When no organic disease can be found in complaints of precordial distress or backache, it is harmful and untrue to say "There is nothing wrong with you. It is just your imagination. Pull yourself together, buck up and forget it." This only causes confusion and resentment in the patient. The fact is that there is something wrong and he knows it. The patient is sick.

A prevalent attitude which influences the diagnosis of a psychiatric disorder is that the patient with a psychogenic disturbance is an unhappy, miserable sort of individual whom no one can like. This is fallacious! The statement has often been made "He can't be neurotic. He is so friendly, so nice and cooperative." Such superficial traits may be entirely deceiving. The severely neurotic individual can be friendly, cooperative and pleasant. On the other hand, an individual with an organic disease without psychogenic components can be an unpleasant, irritable person. Many physicians hesitate to make a diagnosis of neurosis because they feel that so categorizing him is an attack upon the patient's integrity. This, too, is a common error.

Psychiatry differs from other branches of medicine in that treatment begins at the very onset of the diagnostic survey. Accordingly, it is pertinent to this presentation to discuss the harmful effects of overexamination, particularly by laboratory tests. Patients with emotional disorders who present somatic complaints are frequently difficult diagnostic problems. However, by early recognition of the psychiatric components, an exhaustive and fruitless search can be avoided, thereby preventing fixation of the disorder in the patient's mind. Reasonably early decisiveness after careful evaluation of the patient's personality is highly desirable. During the continued diagnostic studies which may be indicated, the patient should be informed that their purpose is for completeness and not because of suspicion of a serious organic disease.

The specialist is particularly prone to the error of seeing the patient from his special viewpoint. For example, in a patient with pain in the right lower quadrant of the abdomen, the gynecologist may make a diagnosis of cystic ovary, the urologist may determine that the patient has

a ptosed kidney, and the surgeon may decide that the patient is suffering from chronic appendicitis

It is true that to remove an appendix from a neurotic individual may do him no great physical harm. Psychic trauma, however, may result. It is a relatively simple procedure. He is in a hospital for ten days, and one can rationalize, "Well, appendicitis may have been responsible for his symptoms. He may as well have it out—and except for the inconvenience caused, no harm has been done." Actually, this is not so. Psychologic harm has been done. The individual may well have been put on the road to polysurgical addiction. The stamp of authority has been placed on his ailments, and he has become certain that his disorder is organic. The chronicity of his ailments is at hand, his usefulness is diminished, and therapy is made more difficult. In the absence of organic disease, such diagnoses and treatment contribute to the fixation of the patient's disorder.

When the patient's disability is out of proportion to the structural change, elective surgery should be very carefully weighed before it is undertaken. In our experience in the military service, we found that elective operative procedures in individuals with moderate to marked superimposed neurotic reactions yielded poor results. Evaluation of the patient's psychologic makeup is indicated in elective surgery.

Sometimes errors in diagnoses are made because the physician is influenced by his own personal reaction to a particular individual. The physician's background, neurotic traits, medical training and even feelings at the moment affect his attitudes. As the doctor increases his diagnostic skill from a psychiatric viewpoint, the need for elaborate defensive method is diminished.

Full realization has been lacking that a great deal of our behavior, feelings, attitude and sensations are determined by psychic processes over which we have no conscious awareness or control. We have learned to accept the activity of a glomerulus even though its function is not evident on the surface. We do not hold the individual responsible for what his glomeruli do, because we are familiar with the anatomical and physiological activity of the renal unit. In a similar way, the personality has structure and function which has been explored and is understood. We speak of a *dynamic* unconscious. With this concept of the unconscious, we can better appreciate the patient's feelings and behavior.

The significance of a psychiatric diagnosis bears further emphasis. Arriving at a diagnosis consists of more than applying a label. The doctor is not content to determine that a patient has pulmonary tuberculosis. He goes further—he evaluates the extent of the tuberculous process, its exact location, and by studying the sedimentation rate, temperature, pulse, respirations and weight loss, he learns the reaction of the whole individual. Similarly, it is insufficient to say that a patient has an anxiety state, without further classification. It is im-

portant to know under what circumstances it occurred, the duration of the disorder, and how it has interfered with his general functions. In the light of these facts, what is the prognosis and how long will it take? For some time it has been a practice in progressive psychiatric centers and clinics to make a dynamic detailed diagnosis, comparable to that utilized in cardiology. In June, 1945, the Surgeon General's Office published Circular Letter No. 179, which clearly discussed the proper method to be followed in making a psychiatric diagnosis. This diagnosis consists of four parts:

- (1) The type and severity of symptoms
- (2) External precipitating stress
- (3) The premorbid personality and predisposition
- (4) Degree of its incapacity

A fifth item might be added to give depth to the diagnosis, namely, the purpose served the patient by his neurosis.

In order to state the diagnosis in this fashion, the physician is compelled to have a better knowledge of his patients. Such a complete diagnosis indicates that the disorder is an active process which is occurring in a particular type of individual who has reacted with an emotional illness to certain stresses, for specific reasons.

During the war the need for psychiatric understanding and approach was so great as to cause particularly marked emphasis on this topic. In many quarters the subject was overemphasized and incorrectly presented with the result that there has developed a good deal of justifiable criticism of the excessive erroneous diagnoses of neuroses. The error will occur less frequently, however, as the etiology, structure, manifestation and methods of evaluation become more familiar to the physician. A mature, objective, understanding attitude is the most important single factor necessary for correct diagnosis. Being oversympathetic or undersympathetic is equally as undesirable and deleterious to the doctor's skill.

An unbiased, alert awareness of the problem and an adequate realization of the functions of a dynamic unconscious will in themselves make it possible for the physician to recognize and deal more effectively with his patients who have emotional disorders.

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THE TREATMENT OF THE NEUROPSYCHIATRIC PATIENT IN AN ARMY HOSPITAL

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A discussion of *treatment* in a neuropsychiatric hospital suggests redundancy by its very title, which may be analyzed as "treatment in a hospital for treatment of the psyche." The full title, however, while it states the range and scope of the hospital in the performance of its mission, likewise postulates special considerations applicable to the military situation. As a matter of fact, one must speak not only of a military hospital but of "which military hospital?", "where does it operate?", and "how does it operate?"

In this discussion, there will be little of hospitals in forward echelons. In each of these, moving back in theaters of operations, from collecting station to evacuation and general hospitals, each unit performed the primary duty of caring for its psychiatric emergencies from the viewpoint of prompt restoration to duty, or equally prompt removal from the zone in which the hospital operated. In these forward zones the rapid and sometimes more spectacular forms of treatment such as hypno-analysis, narco analysis, prolonged sedation and the like were largely employed—and with much success. As the failures of these procedures became evident, the patients were moved back, and more complex and elaborate procedures were instituted or reapplied until the criteria for success or failure were acceptably fulfilled.

In an overseas general hospital, if the patient was found not likely to be of further use in the theater of operations, or communications zone, he was returned to the United States for further care and disposition. Immediately on return, classification of the patient and his prompt transfer to a neuropsychiatric hospital or a neuropsychiatric center was effected. An important consideration in this transfer was the restoration of the patient to some degree of proximity to his home with the possible healing effects to be expected from this proximity. The ultimate program at the general hospital of the Zone of the Interior, commonly known as a "named" general hospital, was then initiated.

AIM AND SCOPE OF THE ARMY GENERAL HOSPITAL

At this point, pause should be taken to determine the objectives of this hospital—the "named" general hospital. In an ordinary psychiatric

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hospital, the obvious mission is the full expression of all the implications in the word psychiatry—"treatment of the psyche." Time is of the essence, but not the utmost essential. Were this to be accepted as the essential mission of an Army hospital, the multiplication of Army hospitals would then be endless and each hospital would become stabilized at the level of its residual population.

First, then, must be recognized the fact that the Army hospital in the Zone of the Interior is a step in the performance of the military function of caring for the soldier—a final step. On the other hand, it must be recognized that the nation, that is the community at large, from which this soldier came, is the source of the Army, its personnel and its patients, that the military force is only the means with which the nation at large fights its wars, that it is an agency of the United States, that eventually, the Army in its present form will no longer exist, and in the same way as its soldiers will become civilians, so its military patients may become civilian patients, in some instances.

Briefly, then, the Army is not the ultimate repository for those who have suffered the misfortunes of a war which has been fought for the country at large. From this thesis derives a fundamental restriction of the sphere of activity of a military hospital, namely, that when a militarily incurred disorder reaches a stabilized phase, the hospital must relieve itself of responsibility for the patient in order to continue to function on an active level.

Determination of stabilization or chronicity in neuropsychiatric disorders largely involves estimations of time and expectancy, as well as rate of change in the individual. It has been found that the majority of patients who will respond to present known methods of treatment to a degree sufficient to relieve them of the necessity of further hospital care, will do so within an approximate time of eight to ten weeks. Therefore, one criterion for the determination of the maximum period of hospitalization is founded on the condition of the patient at the end of approximately two months. The total period is actually longer, since it includes overseas hospitalization.

A second determinant necessary for the efficient promulgation of the hospital program is the clear recognition and acceptance of the goal. As previously stated, the ultimate goal of psychiatry is the *cure* of the patient—a goal not as frequently attained as is desirable. To perform the military function as previously outlined, this goal must be restricted.

In its narrowest sense, the function of a military hospital is to bring a soldier to a state of recovery and return him to duty. This cannot be as readily predicted for the psychiatric patient as it can be for the medical or surgical, and, therefore, cannot stand alone as the single objective of treatment, nor of course, would it be desirable on humanitarian grounds. It is, therefore, restricted to the return to duty of the soldier, or if this is not feasible, return to civil life, in the best pos-

sible physical and mental condition, with appropriate advice for future care or appropriate provision for future care, as the case may be

The worthwhileness of these objectives may be subject to argument, but by the acceptance of these limitations, it has been possible for military hospitals to carry out their functions continuously, without necessitating an undue increase in hospital facilities and yet restoring a very large number of patients to the community in a condition at least as good as when they entered military service. To accept less than the restrictions mentioned would result in a bootless struggle for unattainable ends and a definite reduction in the functioning capacity of the hospital.

GOALS OF TREATMENT

The same considerations limiting the aim and scope of treatment are pertinent likewise in limiting the forms of therapy which must include those methods which can be expected to be effective within a reasonable period of time, though it is not necessarily to be expected that the maximum effects of therapy will be apparent within the specified time.

Therapeutic techniques in psychiatry have as their ultimate goal the cure of the patient—the removal of inefficient methods of dealing with life problems and the education of the patient in more efficient methods. This is a limitless objective, and the criteria for the judgment of its achievement are so many and so complex that unless simplification is achieved, it might again become unattainable.

Here must be considered one of the major difficulties in psychiatric practice anywhere, and one which is sharply emphasized in military neuropsychiatry—personnel. There are not nearly enough psychiatrists; there are still fewer well-trained psychiatrists; psychiatric nurses are at a premium and psychiatric attendants must be created. Individualization of patients when thousands are involved is most difficult. Wherever possible, methods and techniques must be organized for application to groups and classes. Since unsoundness in categorical definition may lead to serious defects in treatment, methods of generally universal applicability are desirable.

This need has led perhaps, to an oversimplification of the goal of treatment. Acceptance of this simplification does not of course imply essential naiveté on the part of the therapist. He recognizes the complex facets of personality functioning in the individual. On the other hand if he can modify an outstanding aspect of personality dysfunction which is universally applicable it cannot but affect other aspects of personality dysfunction. Overcategorization such as an overattention to nomenclature and semantic distinctions will necessarily defeat a broad program of treatment directed at large masses and groups.

Let us examine the essential make up of a mental or emotional disorder. These two great categories represent a separation, largely into psychosis and nonpsychosis, a distinction which is striking on the sur-

face, but far from obvious when reduced to the fundamental dynamics underlying the reaction patterns. For working purposes, we may accept the fact that both mental and emotional disorders are intrapsychic therapeutic efforts. Inefficient as they may be from the viewpoint of social adjustment, they act to prevent the complete emergence of an underlying disturbance which, if allowed full expression, would be considerably more painful than the explicit symptoms. In other words, symptoms of a psychiatric disorder represent an effort to reduce unbearable anxiety.

This simplified concept of functional symptoms would lead to the conclusion that the external effect of symptoms must necessarily lead to an improved condition in the individual. Intrapsychically, this is probably true. To the observer, who sees the effect of symptoms only in the relationship of the patient to his environment and the performance of said patient within a postulated framework of behavior, conation and cognition, the effect of the symptoms, if they do reduce anxiety, is not at all a restoration of the patient to a community of interest with the world, but, on the contrary, a separation of this individual from the world, in which without obvious or discernible disturbances in his physiological or physical economy he appears to differ from other men, to perceive differently, to feel differently, to act differently—to be different. In summation, the symptoms have served the function of isolating the individual from others by the imposition of an involuntary, unrecognized and inefficient autotherapeutic process.

This evaluation of the ultimate effect of psychiatric disorder is an oversimplification, as we have said. It does present, however, such a large common denominator for most disorders, that it may be made to serve as the keystone of the treatment program—and it does. Indeed, as we shall see, it is the fundamental basis of the group therapy program. In a hospital such as the military one, all therapy in a large sense may be considered group therapy, when one sees the general similarity of large groups of disorders and the basic objective of breaking down the barrier of self-imposed isolation that we have described as a common denominator of functional disorders.

The prime purpose of freeing the patient from his self-imposed isolation, if accepted as basic, serves also to establish the organization of the entire treatment program. It serves automatically to place the patient in his proper sphere of performance, from which level the nature and extent of treatment follow. With large numbers of patients, more is accomplished for each individual by this means than by overindividualization and categorization based on close similarities.

GENERALIZATIONS ABOUT TREATMENT

First, a few generalizations about treatment, whatever the type, whatever the aim, are indicated.

Indoctrination of Personnel—Treatment begins with a thorough

grounding and indoctrination of all personnel in the fundamental goals and objectives of the program. This follows, naturally, for medical nursing and attending personnel. It goes much further, however, and the indoctrination program should include such diverse elements as finance personnel, mess attendants, military police and, indeed every person who is a part of the hospital and plays however remote a role in the direct performance of its mission.

Reception of the Patient—The entry of the patient into the hospital, from the time of his debarkation to his reception on the ward, is critical. When patients arrive from the various overseas sources, they are tired and often quite irritable, some are psychotic. They arrive in many states of mind and activity. Many have souvenirs which mean much to them. Others have souvenirs which mean much to them, but also to others, such toys as live alligators, loaded weapons and the like, with their various potentialities. These must be taken away and the soldier appreciates quite begrudgingly why he must conform to the needs of the group and surrender his prized possessions. Obviously, these possessions *can* be taken by force. The method by which they are obtained may serve to abate the original resentment and hostility, or may serve to increase them. The man who performs this task has become a therapist.

An attractive Receiving Office with pictures on the wall, some gaiety, lightness and cleanliness begin to spell comfort and welcome. Attention to simple wants like cigarettes, cokes or coffee, served by attractive and well trained assistants, such as Red Cross workers and Gray Ladies, send the patient somewhat more tractably to the Admitting Ward.

Whether it be true or not, many Army neuropsychiatric patients claim not to know why they are in a hospital. There is no doubt that many of these professions of ignorance are without factual validity, and are denials of psychic illness. In acceptance of this thesis, however, lies a great danger that the patient will be challenged and antagonism enhanced. Therefore, each group is told clearly and in simple terms why they are in the hospital and what to expect.

Classification—Within the space of an hour the entering patient is interviewed by a psychiatrist and classified for open, closed or disturbed wards. It should be noted that the diagnosis is of less importance than the basis on which this classification is made and the problems to be solved. An open ward patient (Group A) is one considered fully capable of cooperating voluntarily in the program to be outlined for him. The closed ward patient (Group B) is one of whom some doubts may exist and who will require longer observation to establish his status. The disturbed patient (Group C) is one who is reacting beyond the bounds of sensible behavior or who is believed likely to act in this fashion.

His Orientation—The first step of individual treatment of the pa-

tient occurs in the admission ward with the interview by a psychiatrist and the initial classification of the patient. The patient is informed of steps to be taken and the outlook—orally and in an orientation booklet. It is well known that the next day some of them will say they were not told, and will profess not to have seen a doctor and to be in complete ignorance of the reasons for hospitalization and of future expectations. Patient repetition and full knowledge on the part of all personnel will eventually break this attitude down—for an attitude like this is an expression of anxiety, and defensive challenge—a denial of painful truth. So are many tales of mistreatment.

PROGRAM FOR THE OPEN WARD OR CONVALESCENT PATIENT

From this point, the treatment of the patient is reversed, in that the hospitalization consists of a series of stages beginning not so much with the illness and ending with a convalescence, but with the converse, and the full hospital program is developed about the so-called convalescent patient. The epitome will be the patient on an open ward. In most instances, he will have a psychoneurosis, probably with mild trends exhibited in his premilitary life. He may or may not have been in combat. There may be a definite personality defect underlying his symptoms. He may have a psychosis, or a psychotic-like reaction in remission. He will have been returned to the Zone of the Interior, because overseas, intensive treatment has failed to restore him to a duty status.

Reconditioning—The groundwork pattern for treatment of this patient, who already shows his capacity for resocialization, is called *reconditioning*. All phases of reconditioning have the same purpose of making a patient a functioning part of the community with a normal balance of interests and activities. He will have occupational reconditioning for one and a half to two hours daily. His activities, of which he may choose the specific, but not the general, run the full gamut of resources of a well-equipped shop, such as plastics, carpentry, photography, ceramics, metal work, and so on. Emphasis is placed on the practical technical pursuits which will be of value in the event of return to civil life.

Another one and a half to two hours is devoted to educational pursuits, ranging from business English to radio announcing, salesmanship and music. A third similar period involves physical reconditioning with a variety of activities, emphasis of course being placed on group activities and games, rather than on formal exercises. This is carried on outdoors wherever possible. The number of special occasions, such as swimming, fishing, golf, horseback riding, serve to maintain a normal and informal variety and dispel the appearance of regimentation and mass treatment.

Patients in this "A" group just described have attendance cards and on the basis of these cards secondary gains such as passes are predi-

cated. This also aids in promoting good and regular habits, and little difficulty is incurred in getting good attendance from most patients.

From the general program of reconditioning are selected special activities within the various categories. Special aptitudes and interests may be considered as they become apparent during the course of the routine activities. While each ward has its own ball team, there is an all-star team. While most patients have the information and education activities, selections are made for performers in the daily radio show which is prepared by the patients and broadcast to all wards. The hospital newspaper for patients and personnel serves an excellent outlet for active participation and as a universal source of passive participation. The central radio broadcasting system serves a similar purpose. A large number of the open ward patients participate every Friday in a formal retreat parade—in full uniform. Here the use of a thoroughly ingrained new culture as well as old attitudes and interests becomes the nucleus on which socialization is organized.

Whether he is to return to civil life or not, the patient is expected to continue to be a good soldier, that is, a good citizen, as his contribution to treatment. This consists not only of attendance at retreat parade, a formal expression of military participation, but of as much participation in the job of running the hospital as is considered desirable. Assistance in maintenance of the ward and in messes as well as in specialized jobs for which certain individuals may be especially fitted, represent cooperative citizenship with other patients and with the hospital as a whole, as well as a contribution to economical administration of the hospital and treatment. There is no mental stigma to honest work of any sort. Many patients actually enjoy this as a form of cooperative endeavor.

Individual exceptions are made, of course, but always under the approval and guidance of the medical officer. The execution of this program always under the professional aegis of the neuropsychiatric service, is carried out by men and women especially trained in all phases of these activities and oriented to the special psychiatric approach.

Encouragement to grouping and sharing of interests is constantly present. From a common interest with one person such as a two man project in occupational therapy, to competition between wards or other units, in which the personnel also participate, there is ceaseless stimulation towards an increased participation with larger and larger groups.

Evenings are given to entertainment provided from many different sources and much is provided by the participation of the patients themselves, activity rather than passivity, group rather than individual being the constant aim.

The use of female personnel in this male atmosphere is important not only on the social side such as dances and parties but in the

effort to reduce the overmasculinized attitude characteristic of Army organizations, and the restoration towards a more balanced social viewpoint which will mark the future civilian life

Patients in the A group are entered in the reconditioning program immediately they are assigned to wards, without too many preliminaries concerned with basic selection or an overrefinement of the criteria of selection. After the preliminary examinations, mental and physical, other special examinations, including indicated laboratory work, psychological studies, social histories and beginning approach by the social worker towards future problems all are insinuated in each individual case by temporary excuses from one or another project of the program, as may be required in the individual case.

Visiting by relatives and friends is of tremendous importance, and a definite part of treatment. This must be balanced, and is achieved by limitation of visits to three afternoons a week, one during the week, the other two on week ends when activities are reduced.

During the course of the next six or eight weeks, the patient will have a number of private interviews with the social worker and a number of individual interviews with the medical officer in charge of his case. A few who require considerable individual treatment will have regular discussions throughout their stay. Regular daily rounds by medical officers serve to care for administrative features of treatment. These must never be omitted and all patients must be present. The interchange of problems, "gripes" and their prompt and energetic handling are most important.

Group Psychotherapy—Specialized psychotherapy is subsumed under the heading of "group therapy." On each ward, from the very beginning of the patient's stay, a group therapy session is held each week, attendance of patients and personnel being required. This level is called the PSW (psychiatric social worker) level and the discussion is conducted and mediated by a specially trained psychologist or psychiatric social worker. The defined approach in this group of sessions is at the realistic and practical. A series of selected subjects comprise a "course" of six to eight discussions, such as "The G I Bill of Rights," "My Illness and Myself," "What of the Future?" and so on. As is to be expected in any group session, the subject is generally a point of departure for an open discussion of many patient problems. The "give and take" in these sessions serves not only to abreact much anxiety, often expressed as a hostility, and to correct a great deal of misinformation which seems to exist among average soldiers, but also tends to leaven and homogenize the group.

It was at first felt that these groups must be carefully selected, but as experience was gained it was found that dissident elements could serve, if reasonably well controlled, an excellent purpose in caricaturing defective attitudes for the common good and that even the dissidents quite frequently benefited. The use of a ward unit as a basis

of the group was found to be quite satisfactory, even though the groups were quite large, containing as many as forty participants. A by-product of these sessions is a constant insight which could be of assistance in correcting, where possible, hospital procedure.

A consideration in these group therapy sessions was the necessity of recognizing that in any psychiatric treatment the results of treatment are by no means apparent during the course of therapy. The recognition of fundamental knowledge of psychodynamics to improve the group program was essential in the early days, when it appeared that hostility in anxiety patients was not promptly abreacted with the discussions. It was necessary that the therapists learn that overpassiveness and overcompliance was a more significant signal of ineffective therapy than was overaggressiveness and hostility. As the analysis of resistance came to be recognized as important, the effectiveness of the sessions became much more apparent as was shown in patient-attitude surveys taken at the time of departure from the hospital. Another important by-product of these group therapy sessions is the selection of individual cases for special attention by the medical officer or the social worker, as the case might require.

Once a week, also, each medical officer holds sessions on his own ward, the general object being the discovery and discussion of emotional illnesses besetting the patient. In contrast to the PSW sessions, these discussions are directed definitely at the patients' symptoms. The attack will vary on occasion from an exchange and illumination of experiences under the mediation of the medical officer to brief talks on a mental hygiene level. In any case, as with the social worker, the clarification of misinformation, increased understanding of the individual, his symptoms, his problems, are primary goals. By the commonality of experiences seen in these discussions, group therapy again serves to break down the self-imposed isolation of the patient, and to assist him in coming somewhat closer to the "modal" individual.

From the WO (ward officer) level just presented, will be selected patients for special therapy in the Sp (special) groups. These groups are smaller than any of the preceding and are selected on the basis of similarity of background, experience and reaction. Battle casualties and nonbattle casualties do not mix well when discussion of emotional disorders is to reach very deep into the personality, nor will an urban lawyer have much in common with a mountaineer, though their illnesses are similar. There are many other common and dangerous considerations. The Sp discussions are conducted by the best trained psychiatrists, often analytically oriented.

While group therapy techniques were first adopted because of the need for bringing psychotherapy to as many individuals as possible, it is now apparent that these techniques have an inherent value of their own, and are by no means to be considered as substitutes for the deficiency of personnel or inability to bring adequate individual therapy

to all patients. Individual therapy in the general hospital is quite necessary, but even when possible to a very great extent, it does not supplant group therapy. A patient under expert guidance will often more readily accept the explanations of his buddies in preference to the intellectual explanation of a psychiatrist. These men are men with whom he is identified in health and in illness and they will mutually support each other as they did so powerfully in the stress of combat.

Programs quite similar in their general outline to the foregoing are devised for female patients and also for officers. In these instances, the differentiation inherent in either the status of the individual or his rank provides a generally uniform modal value for the group.

The program thus outlined will care for the treatment needs of a great proportion of the patients, and with the individual therapy derived from the ward officer interviews, social work planning, special testing, such as various psychological procedures (Rorschach, TAT, vocational aptitude, and so forth) is effective to an extensive degree.

Application of Group A Program to Cases of More Grossly Apparent Disorder—Group A, as is to be expected, will be composed of anxiety reactions, many somatic syndromes, remitted psychoses, a few anancastic states, and related types of reactions which are expressed almost entirely in a subjective manner. Between Group A and Group B is a melange of cases of which the expression is outward and rather grossly apparent. This group includes such cases as diverse forms of hysteria, symptomatic stuttering, tics, severe tremors, paralyses, dyskinesias, dysaesthesias and amnesias. All of these cases are susceptible to the full approach of the Group A program except for the limitations imposed by the special disorder. Heretofore, the symptomatic treatment of these types of disorders has been rather interdicted in favor of attacking the underlying dynamic disorder. This is desirable but unfortunately quite time-consuming. It has been found practical to treat these symptoms directly, combining with the symptomatic relief a concurrent attack on the individual dynamics. Hypnosis and narco-synthesis are the chosen means, with sometimes a combination of the two in resistant cases. In these latter instances the patient's first treatment will consist of revelatory analysis under sodium amytal or pentothal followed by the induction of hypnosis and posthypnotic suggestion for future use. When a good hypnotic manipulator is present, it is feasible for him to carry out rapid techniques and transfer the cases to other therapists for continuation. In any case, it has been found that the revelation of dynamic difficulties under either of the above procedures has quite generally led to a marked symptomatic relief permitting the patient to enter the full program at once and continue this treatment at the level of Group A. Sometimes a number of treatments, particularly in the amnesias and conversions, is carried along as the rest of the program goes on.

PROGRAMS FOR THE CLOSED AND DISTURBED WARDS

Group B comprises the intermediate class of closed ward patients. These are largely psychotics in a relatively nonreactive phase of their disturbance, but still requiring supervision and guidance, still unable to function independently. A few severe psychoneurotics, usually of the depressive type, are included. Group B is carried through a program similar in all respects to that for Group A, except for the Sp level of group therapy, which is conducted only for closed ward officers. These patients are taken to all their activities by attendants. Activities off the ward are encouraged, in fact, provided to the same degree as for patients in Group A. By persuasion and example these patients are led into very active participation and in many instances will excel the participation level of Group A patients. Held before these patients is the inducement of open ward with its freedom and privileges. The Group B phase of treatment is not infrequently a very short one from which patients move quickly to Group A.

Group C is composed almost entirely of patients with very active psychoses, acute excitements, depressions, catatonias, and so on. No one of these is considered beyond access or treatment. Immediate treatment needs of this group are provided by hydrotherapy in the form of continuous baths or wet sheet packs as may be required. A high percentage will receive electroshock therapy.

The wards on which Group C patients are housed are usually paired with provision for one of the paired wards to have patients on an improved treatment status. This has been found effective in allowing greater freedom of classification of patients within the group and ready trial on improved status. The better of the two wards has finer furniture, its own radio sets in addition to the general broadcasting system, and even television sets. This is a great inducement to patients on the more disturbed wards towards adjustment and recovery. Patients on the improved ward are handled in groups, as against the individual treatment of the cases on the very disturbed wards. At each step, as has been repeatedly emphasized, attempts are made to lure the patient into a community of interest with others.

SHOCK THERAPY NARCOSIS

Shock therapy, like the other forms of treatment, is directed at the symptomatic expression of the patient and cases are no longer selected according to diagnostic categories. The general criteria of reactivity, acuteness of onset, relation to reality problems, all of which are well recognized as indicating a good prognosis, are generally found in Army patients. In addition, the criteria established by Simon and Holt are used as a guide for the selection of cases. Certain symptoms such as refusal of food, confusion and bewilderment, disorientation, depression and mutism indicate a good prognosis for electrotherapy. Others such as inappropriate affect, bizarre speech, euphoria and underactivity

are less responsive. Secondary projections respond well, primary projections do not. Selection of patients by these criteria has led to outstanding success.

Of paramount importance is the necessity of instituting treatment early. Many patients will be under electrotherapy within a matter of forty-eight hours. Treatment must be thorough and complete. Great danger lies in terminating treatment at the critical point of about the sixth treatment, when the patient appears to be markedly improved—and usually is. Termination of treatment at this point will result in frequent relapses and many failures. In general, treatment should be carried on until the patient shows no further changes in reaction for the better or the worse. Treatments will range from twelve to sixteen. Just as soon as the patient is able to be moved into the improved treatment ward he should be in full program as laid down for Group B.

Patients and relatives should be reassured concerning memory defects which are the common temporary sequelae of shock therapy. With the present organization described, this is almost unnecessary. Patients under shock therapy are so utterly aware of their own improvement they form their own groups and pass these considerations along so that they are found to be the best informed concerning their own treatment of any group. At times, they speak and write of themselves in a rather humorous vein.

A few cases which cannot for physical reasons be treated with shock therapy may be given prolonged narcosis. This form of treatment requires the same attention to completeness as does shock therapy. An essential is constant nursing care and a sleep chart, the goal being induction of narcosis by intravenous sodium amytal and its continuation by oral or nasal route to the degree necessary to maintain a sleep rhythm of four to five hours before waking appears. This may require enormous doses of the drug when carried out for a continuous period of two weeks. With proper feeding and nursing care in the intervals when waking begins and remedication is taking effect, many cases which would otherwise exhaust themselves may be brought to a much more satisfactory level of hospital adjustment and improvement—sometimes recovery.

Insulin coma as a form of psychiatric treatment has been generally impractical in the military service because of the extensive nursing requirements and the need for constant medical supervision. On a statistical basis it offers no more, and perhaps less, than does electroshock therapy. In a few cases, the use of small doses of insulin to assist in the improvement of nutrition is desirable.

DISCHARGE AND FOLLOW-UP

Approximately two months of any of the programs outlined will bring the great majority of military patients to the point of so-called

'maximal benefit of hospital care." At this point most neuropsychiatric patients, while they may no longer be suitable for military life will be quite able to resume their previous civilian status without anticipation of psychiatric difficulties. Those in Group A will generally be able to assume their old positions in the community. Some of those in Group B will also be able to do so. Some will be suitable for discharge with some degree of supervision by relatives and continuation of convalescence at home. Many Group B cases will have progressed to Group A as will many cases in Group C. For all these patients further hospitalization is likely to be more detrimental than beneficial. The tendency to fix symptoms by overemphasis must be counteracted and a stop made at "well enough" rather than at perfection. The tendency of treatment effects to continue beyond the period of active treatment is well recognized and should always be considered in the termination of hospital stay. In a sense, discharge from the hospital constitutes treatment. The few patients who remain (since full organization of the treatment program, this number has been very small) will require further hospitalization indefinitely, either as chronic cases or slow convalescents and will go to veterans' hospitals. A few of the Group B cases will remain chronic but many of these patients will improve at home to a level equal to their best pre-military adjustment.

Every patient who is discharged from the hospital for medical reasons is given an opportunity to have further care at a Veterans Administration Facility. Patients in Group A make this decision voluntarily and almost universally decline the privilege, believing themselves quite able to assume responsibility for the future. Patients in Group B are taken under military escort to the homes of their relatives if the relative desires to assume further care, with the expressed right to have veterans' hospitalization whenever required in the future. A few patients for whom continued care at a veterans' hospital is deemed absolutely necessary are transferred to such hospitals near their homes and discharged from the military service.

In all cases, whether the soldier is to be returned to duty or not, treatment has included plans for the future. The social worker will have worked out problems of special importance to each individual in making his restoration to the community more successful. He will advise the patient of community resources which he can tap not generally, but specifically in relation to his own community. If the psychiatrist feels that further outpatient treatment is desirable he will refer the patient to the particular agency in his community equipped to perform this function. Psychologists will perform vocational aptitude and other tests designed to help the patient in choice of new vocations or restoration to old. The Separation Department will have assisted the patient in making out all claims for pensions and benefits to which he might be entitled. The United States Employment Service

and Civil Service have helped in job selection and placement. Separation counsellors, legal assistance officers and others have paved the way for a full restoration to civil life. It is important at this point, however, that the patient now brought to a level of community functioning, be kept self-reliant and be prevented from developing a sense of dependence which could readily arise out of so much guidance. A most dangerous consequence of the social guidance of the patient may be the tendency to make him overdependent on external agencies and dependent on his military rights and benefits.

It cannot be overemphasized that the period of treatment in the military hospital is a period of reconversion and until he leaves the hospital and returns to the community, the patient is not yet a civilian. It must also be reiterated that the hospital is performing an intermediate task in the reconversion of the patient, a task which the community must take up the day he leaves. In most instances, he will be well enough to carry his own responsibilities, but where he is not, the attitude of blaming the Army is unreasonable and unjust, since the Army is performing one phase of the total job of the successful pursuit of the war, and the return to peace. Nothing which has happened can be considered to have changed this individual any more than he would have been changed by the process of living and maturation. Unless he receives full opportunity on a level with his peers the fruits of all the labor which has gone into his restoration will be lost.

It is the duty of all those whom this former soldier will meet and know to see him as he actually is—a man who has been away and has come back. He should be welcome.

PSYCHOLOGICAL ASPECTS OF THE PARAPLEGIC PATIENT

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This study was undertaken to determine the nature of the process of adjustment in the paraplegic patient and to focus attention upon the psychological and personality factors which affect this process. The problem of rehabilitation of the paraplegic patient while it is by no means a new one demands greater consideration because of the larger number of patients who incurred this disability in World War II

It is estimated that there are between 1200 and 1400 paraplegic patients in Army hospitals at this time. These men have been salvaged by modern medical and surgical skills and techniques which were not available during World War I. Rapid and efficient evacuation of the wounded, measures to counter shock, sulfonamides, penicillin and streptomycin, and greater knowledge of nutritional management have restored to physiological balance many who formerly would have perished. If these men are to be something more than a living memorial to the skill of medicine, the task of rehabilitation must be attacked with similar aggressiveness.

The paraplegic patient is confronted with the colossal task of meeting everyday problems in spite of the severe handicaps of residual disability. Acts formerly performed in an unthinking and automatic fashion now represent challenges to functionless nerve pathways and unresponsive joints and muscles. Getting out of bed, evacuation of bladder and bowels, ambulation and the most elementary forms of self-care must all be relearned arduously and often with physical equipment inadequate for the task. It is not surprising that psychological factors enter largely into this process of adjustment.

While those who have undertaken the care and management of the paraplegic patient have shown an awareness of the problem and have evolved satisfactory techniques to cope with it, little material has been published on this topic. A review of the literature since World War I does not throw light on the personal and interpersonal relationships which set the paraplegic apart from other groups of physically handicapped. There are several studies, generally introspective and autobiographical, relating to the psychology and the adjustment of the

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physically handicapped. These for the most part have been written by persons who have been themselves exceptionally well adjusted. This adjustment potential is not innate and not easily acquired and deserves further investigation.

The type of onset in paraplegia is of considerable psychological importance and requires comment. The symptomatology and incapacity are at their height at the time of injury and a reasonable expectation can be held that the condition will not become worse with time. The nonprogressiveness of the traumatic injury as compared with a chronic degenerative disease such as multiple sclerosis is a factor of fundamental psychological importance. The patient is not necessarily subjected to the extreme emotional swings which occur with the remissions and exacerbations of an active disease process. At the same time he is denied the self-deception of delayed integration of the physical disability. The ego must absorb at one time wounding, shock, infection, prolonged illness, as well as crippling of body, sex functions, bladder function and personality. This realization cannot be reached without profound disturbance of the ego nor without considerable situational depression.

The group studied represented a fair sample of the Army population in general. It consisted of 109 male soldiers at Halloran General Hospital, six of whom were officers and the remainder enlisted men. The ages ranged from 19 to 39, 75 per cent of the patients being thirty years old or younger. General mental ability of the group as determined by AGCT scores on induction ranged from low scores in Grade IV to high scores in Grade I showing no concentration of scores at any level. Educational background ranged from five years of elementary school to graduation from college, the greatest number of men having completed either elementary or high school. Nearly half of the group was married.

In approximately 77 per cent of the cases their prewar civilian occupations required the use of their legs. Of the remainder engaged in sedentary occupations 40 per cent were still students.

All the cases were traumatic in origin except for the one case of poliomyelitis and one of neoplasm. The duration of illness at the time of the study ranged from three to twenty-seven months, the average being nine months. Seven had been disabled less than six months, eighty-nine six to twelve months and the remainder more than twelve months.

The cord lesions ranged from concussion to transection, the levels of injury from the sixth cervical segment to the sacral segments and included several cases of cauda equina injury. There were seven cases of injury to the cervical cord, fifty-two cases with injury to the dorsal cord and forty-two cases with injury to the lumbar cord.

The group studied included patients in the earliest stage of recovery, the intermediate stage and the late stage. In the earliest stages are those patients confined to bed, requiring suprapubic or indwelling catheters,

treatment of decubitus, chemotherapy and nutritional management. In the intermediate stages are those patients who are able to be out of bed for a large part of the day in wheel chairs and who are beginning to learn ambulation by means of braces and crutches. In the late stages are those patients who can walk with braces and canes or with canes alone. Seventy-five patients had either reached or had gone beyond the stage of beginning ambulation. All patients had learned some self-care.

The method used in this study consisted of psychiatric interviews of one to one and one-half hours' duration, conferences with physicians, nurses, attendants and technicians engaged in the care of patients, observations of the group during daily activities, informal chats with the patients and informal social intercourse. Projective techniques were attempted but discarded as being of less value than the direct interview. In fact, these patients showed no disposition to participate in any tests which they felt did not have immediate value.

GENERAL PERSONALITY CONSIDERATIONS

These patients prior to injury were finely trained, in excellent physical condition and totally independent. Concurrently with the injury came total dependence, dependence upon others for transport, sustenance and the disposal of bodily excreta. Despite the fact that they found themselves infantile in their dependence there were no psychiatric syndromes in the usual sense of the word. Nor was there a characteristic personality trend or pattern statistically significant for the group. Psychoneurotics, psychopaths and patients of borderline intelligence were relatively few.

Forty-five per cent showed some manifestation of depression either episodic or prolonged. This was always situational and related directly to concern over the disability. There was no significant difference in reaction between those who had been injured in combat and those injured accidentally. Nor was there any significant difference in those who had been injured along with several others and those who were injured while alone. Loss of consciousness at the time of injury did not alter the resulting picture. No patients expressed guilt over the injury and few projected the blame upon others. Most of the patients were willing to consider themselves lucky that they survived the injury. Three patients expressed shame over their appearance. Only one patient had incurred more than one accident prior to the current disability. They all recognized foci of major concern in five spheres: bladder and bowel control, sexual function, ambulation, general medical condition and future economic status. Some had in addition more individual personal problems.

In general the reaction to the disability was better in those patients in whom the pretraumatic personalities were sound. Patients whose pretraumatic personalities were characterized by extraversion, high feeling tone and little intellectualization reacted well to the disability.

Patients who were part of a stable, closely-knit family constellation reacted well to the disability especially if the patients played a minor dependent role in the family. Patients whose pretraumatic personalities were characterized by intense personal effort and ambition experienced greater difficulty in adjustment. They become depressed easily by slowness in progress and readily give way to anger and irritability. Patients in whom psychopathic traits were dominant reacted poorly to the disability. They were inclined to be demanding, least understanding of the needs of others and subject to periods of frustration. Their behavior was characterized by episodes of tantrums, profanity and abuse of the nursing and attending staff.

OTHER PSYCHOLOGICAL CONSIDERATIONS

Dependence—Notable during the period of adjustment of these patients is an increase in their feelings of dependence upon others. The grossly debilitating nature of the injury establishes initially the necessity for dependency but soon this tends to persist beyond the limits of medical necessity and appears rather as a personality phenomenon in itself. Although the patient does not deliberately recognize and consciously accept the fact that much of his former world now has to be mediated through others he has inescapably come to lean upon others even more than his disability requires. The hospital is regarded by many as the one dependable refuge where their needs are best understood and most completely satisfied. It is not uncommon to find patients even more disturbed than resentful when they overhear conversations among duty personnel about being discharged. They fear they might be abandoned and in fact even show disturbance as a result of changes in the personnel who attend them.

Although the hospital satisfies this general insecurity and dependence, proximity to home is a factor probably of equal importance. Receiving frequent visits from their family and in the case of ambulatory patients going home for weekends also offer the patient the emotional solace of easy transference and identification. However, this is not free from psychological hazards. The patient's reaction to obviously overindulgent pity and regard whether it be from parent or from people in general is not a pleasant one. It were as though the patient reacted not to the pity offered him but rather to its implications, namely, the disastrous and hopeless nature of his predicament. On the other hand, he reacts just as unfavorably to neglect and disregard. Although it would be extremely difficult to prescribe a formula for appropriate family behavior and attitudes for the paraplegic, general tact cannot be over-emphasized.

Perhaps the most outstanding single expression of their dependence is revealed in the way these patients consider the future. In many of them one finds the complete absence of any attempt to solve the problems of occupational adjustment and the development of economic

security. Of course, for some of these men this need will be ruled out medically. But for many others, the necessity will arise and, despite this fact, they have implicitly come to accept themselves as charges whose maintenance will be accomplished by hospitalization, compensation and a solicitous family. Others who are equally dependent even if somewhat more aggressive or outgoing about it refer to some mythical business partner they will develop, through whom financial success will be achieved. As one might expect, the amount of individual variation extends also to those who plan their adjustment to the future along more realistic lines. In general, however, the patient's dependence upon others finds another facet of expression in the unrealistic character of his thoughts about the future.

The way in which the patient leans upon others not only for his present adjustment but in his rudimentary considerations of the future as well suggests a type of adjustment frequently recognized as regression. Certain other of his reactions also fit the pattern of regression.

Frustration—Although frustrating experiences of the patients may vary from the most trivial slight to the absolute general blocking of goals, probably the greatest number of experiences of this type occurs in connection with daily ward activities. Typical of these are having to wait one's turn for something or other, being refused something they want, finding part of a meal not as warm as they would like it, not getting the attention they want from a nurse, et cetera. Although reactions to these frustrations vary a type of behavior more characteristic of less maturity than they normally possess is easily recognized as occurring with great frequency. Emotional lability was present more frequently than not. The fine shadings of emotional control were replaced by immature emotional responses. Coincidental with the increase in their feelings of dependence there appears to be a proneness to become aggressive in a fashion compatible with the regression that occurs. There are outbursts of rage, temper tantrums, excessive irritability and impotent anger brought on by the frustration of aims. Evidences of indifference on the part of ward attendants are exaggerated by the patients and bring on bitterness, depression and temper displays. One patient in a fit of rage threw his urinal, another became negativistic and refused to eat, still another patient who was refused a hypodermic sulked and would not get out of bed for his exercises. Attendants will frequently recognize the patients as spoiled, also referring to their petulance and irritability. The patient in many ways also expresses his gripes no differently from soldiers throughout the Army, yet despite this verbal aggression he feels himself ever so much more dependent on the Army than the healthy soldiers.

Another common source of frustration is the great difficulty the patient soon experiences in connection with learning how to use braces and crutches. He frequently loses interest when his progress slows down and develops a protective apathy in his childish rejection of the

Patients who were part of a stable, closely-knit family constellation reacted well to the disability especially if the patients played a minor dependent role in the family. Patients whose pretraumatic personalities were characterized by intense personal effort and ambition experienced greater difficulty in adjustment. They become depressed easily by slowness in progress and readily give way to anger and irritability. Patients in whom psychopathic traits were dominant reacted poorly to the disability. They were inclined to be demanding, least understanding of the needs of others and subject to periods of frustration. Their behavior was characterized by episodes of tantrums, profanity and abuse of the nursing and attending staff.

OTHER PSYCHOLOGICAL CONSIDERATIONS

Dependence—Notable during the period of adjustment of these patients is an increase in their feelings of dependence upon others. The grossly debilitating nature of the injury establishes initially the necessity for dependency but soon this tends to persist beyond the limits of medical necessity and appears rather as a personality phenomenon in itself. Although the patient does not deliberately recognize and consciously accept the fact that much of his former world now has to be mediated through others he has inescapably come to lean upon others even more than his disability requires. The hospital is regarded by many as the one dependable refuge where their needs are best understood and most completely satisfied. It is not uncommon to find patients even more disturbed than resentful when they overhear conversations among duty personnel about being discharged. They fear they might be abandoned and in fact even show disturbance as a result of changes in the personnel who attend them.

Although the hospital satisfies this general insecurity and dependence, proximity to home is a factor probably of equal importance. Receiving frequent visits from their family and in the case of ambulatory patients going home for weekends also offer the patient the emotional solace of easy transference and identification. However, this is not free from psychological hazards. The patient's reaction to obviously overindulgent pity and regard whether it be from parent or from people in general is not a pleasant one. It were as though the patient reacted not to the pity offered him but rather to its implications, namely, the disastrous and hopeless nature of his predicament. On the other hand, he reacts just as unfavorably to neglect and disregard. Although it would be extremely difficult to prescribe a formula for appropriate family behavior and attitudes for the paraplegic, general tact cannot be overemphasized.

Perhaps the most outstanding single expression of their dependence is revealed in the way these patients consider the future. In many of them one finds the complete absence of any attempt to solve the problems of occupational adjustment and the development of economic

security. Of course, for some of these men this need will be ruled out medically. But for many others, the necessity will arise and, despite this fact, they have implicitly come to accept themselves as charges whose maintenance will be accomplished by hospitalization, compensation and a solicitous family. Others who are equally dependent even if somewhat more aggressive or outgoing about it refer to some mythical business partner they will develop, through whom financial success will be achieved. As one might expect, the amount of individual variation extends also to those who plan their adjustment to the future along more realistic lines. In general, however, the patient's dependence upon others finds another facet of expression in the unrealistic character of his thoughts about the future.

The way in which the patient leans upon others not only for his present adjustment but in his rudimentary considerations of the future as well suggests a type of adjustment frequently recognized as regression. Certain other of his reactions also fit the pattern of regression.

Frustration—Although frustrating experiences of the patients may vary from the most trivial slight to the absolute general blocking of goals, probably the greatest number of experiences of this type occurs in connection with daily ward activities. Typical of these are having to wait one's turn for something or other, being refused something they want, finding part of a meal not as warm as they would like it, not getting the attention they want from a nurse, et cetera. Although reactions to these frustrations vary, a type of behavior more characteristic of less maturity than they normally possess is easily recognized as occurring with great frequency. Emotional lability was present more frequently than not. The fine shadings of emotional control were replaced by immature emotional responses. Coincidental with the increase in their feelings of dependence there appears to be a proneness to become aggressive in a fashion compatible with the regression that occurs. There are outbursts of rage, temper tantrums, excessive irritability and impotent anger brought on by the frustration of aims. Evidences of indifference on the part of ward attendants are exaggerated by the patients and bring on bitterness, depression and temper displays. One patient in a fit of rage threw his urinal, another became negativistic and refused to eat, still another patient who was refused a hypodermic sulked and would not get out of bed for his exercises. Attendants will frequently recognize the patients as spoiled, also referring to their petulance and irritability. The patient in many ways also expresses his gripes no differently from soldiers throughout the Army, yet despite this verbal aggression he feels himself ever so much more dependent on the Army than the healthy soldiers.

Another common source of frustration is the great difficulty the patient soon experiences in connection with learning how to use braces and crutches. He frequently loses interest when his progress slows down and develops a protective apathy in his childish rejection of the

major goal. It is a real problem to maintain a high degree of motivation among these men. Patients who begin study courses also frequently lose interest and in general may be said to show an inability to concentrate and hold their attention to any one thing for long.

Autistic Thinking—It is probably safe to say that all of these patients believe that some day they will enjoy a complete recovery of their lost functions. They all cherish this undying hope and it is nurtured in several ways.

In contrast to the amputee who is confronted with the visual fact of loss of an extremity, the paraplegic sees his legs and knows only that they do not move. Sensory changes are interpreted wishfully. The appearance of pain, previously regarded as unpleasant, is now welcomed as a sign of returning function. It is so very difficult for medical officers to make an accurate prognosis that, so far as the patient is concerned, the future remains always pregnant with the possibilities of improvement. The future, in short, is not definitely outlined, it remains structureless, and thus provides the patient with a fertile ground for the projection of his wishes. Patients even occasionally speak of resuming civilian occupations which are entirely incommensurate with the amount of disability. One man has plans of being a barber, another a repair man on telephone switchboards, while a third wants to follow a musical career in a night club band.

This fantasy of future structural integrity is nurtured not only by the inability to provide the patient with a dependable prognosis, but paradoxically enough, also by prognoses at either extreme of the optimism-pessimism scale. The overoptimistic medical officer, who places a premium on the patient's present comfort rather than future adjustment to the incapacities he will suffer, obviously encourages the self-deceptive process already begun by the patient himself. On the other hand, a hard-bitten medical officer who, right from the start, declares flatly to the patient that he will never walk again, frequently has an equally encouraging effect on the patient's rationalizations about the future. Should such a prognosis be wrong and some small gain in motor power be achieved, the patient at once develops the belief that if the doctor were wrong in his first evaluation of his condition, he must be all wrong and that complete recovery is now possible. It appears that the presence even of only one such a case is enough to infect a whole ward and for a period false hope prevails.

The extent to which patients cling to these unrealistic attitudes about their capacities in the future reveals itself also as patients begin to ambulate again. They resist the use of the swing-through gait because "they never walked that way before." Similarly when they are given demonstrations or shown movies illustrating the technic of brace and crutch walking, they are impressed not so much by the fact that ambulation has been attained, but rather by the awkwardness of the gait. This distastefulness of the reality situation is expressed by

resentment among the patients when confronted by someone who has been walking in this fashion for years

The patient's dependence upon time rather than effort for his improvement is still another expression of his autistic thinking. He tends to believe that time itself will result in the recovery of lost functions. "If I knew I were not going to get better, I would work harder on my exercises" is the typical attitude. The lazy confidence these men place in their hopes and expectations, in many cases, militates against the energetic, highly motivated adjustment necessary to realize—even, in part—these desires. By no means do these men willingly accept their allotment of exercise and mat work.

Plans for the future, already mentioned in connection with feelings of dependence, also suffer autistic distortion

DISCUSSION

The life history of paraplegia is not static but should consist of slow uphill progress. In comparison with other chronic diseases in which there is either a plateau, a gradual decline or a series of peaks and valleys coincidental with remissions and exacerbations the paraplegic patient can look forward to considerable physical recovery.

A second factor worthy of discussion is that for the most part the present group of paraplegics in Army hospitals is homogeneous in the sense that the disabilities were all incurred at relatively the same time and that within limits plans for rehabilitation can be based upon the premise that progress will take place in groups of persons rather than in isolated individuals.

In general it might be said that the first six-month period after injury is taken up in preserving life and restoring homeostasis. This is the stage when infections are combated, decubitus ulcers form and heal, urinary control is begun and the ego begins to accept the fact of invalidism. During the second six months the problem of ambulation is attacked and the first faint sparks of motivation are struck. Measures to relieve pain are instituted. Self-care is attained. During the third six months medical and surgical procedures become of lesser importance and rehabilitation assumes greater importance. Certainly not all patients follow this temporal pattern but within limits all go through these stages.

It therefore becomes feasible and even imperative to anticipate the needs of the majority of patients at any one time and to plan effectively well in advance of the need.

In very few instances will these patients be able to compete in an open labor market. The aims of reconditioning therefore, must necessarily go beyond the restoration of the maximal physical and emotional fitness. The task is not finished until a suitable occupational placement has been made and the patient has been trained and followed for a sufficient period to insure success in that placement. The

cooperation of industry must be sought and there is no reason to believe that this cooperation will be wanting. It is not beyond the realm of possibility for an industry conveniently situated to the patient to provide a position commensurate with his vocational aptitudes, mental ability, interest and physical status. The final six months of the patient's hospitalization can then be used to train him for this position. The goal thus provided will focus his attention on what he has retained rather than what he has lost. No other single factor will combat the apathy, dependence and autistic thinking of the patient. No other single factor will provide the motivation so necessary.

Of general significance also is the type of personnel selected for paraplegic wards. The positive and negative effects of nurses and attendants upon patients are too well known to be repeated here. The effect the patient may have upon the attendant, however, is not so well recognized. It is a distinct emotional shock to meet with and care for paraplegic patients. This is usually experienced as a kind of depression. One hears expressions such as, "I feel as if I'm carrying around a heavy weight." One person described anorexia for several days after assignment to a paraplegic ward. Others admit easy irritability or a complementary attitude of excessive sympathy. This shock wears off as the understanding of the condition is integrated into the psyche and as rapport is established with the patients. The inadvisability of frequent changes of personnel is, therefore, apparent.

The obligation of the physician to the patient goes beyond specialized medical care. Although the most skilled neurosurgery, genitourinary surgery, plastic surgery, medical and nutritional management are obviously essential there is a danger that the sum of these parts is taken to be the whole. It is not sufficient to provide the most competent specialists. An understanding physician to maintain liaison is still necessary. The patient must be treated as a whole. He needs someone with whom he can talk over his problems and on occasion he requires the assistance of a trained psychiatrist.

SUMMARY

- 1 An exploratory study of the psychology of a group of 109 paraplegic patients has been made.
- 2 Although no psychiatric syndromes in the usual sense of the term were found, the presence of feelings of dependence, depression and autistic thinking has been recognized.
- 3 The reaction to the disability as a function of general personality structure has been described.
- 4 Recommendations have been made for rehabilitation measures going beyond specific medical and surgical treatment.

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SYMPOSIUM ON RHEUMATIC DISEASES

FOREWORD

ARTHRITIS and rheumatic fever continue to be major problems in the field of internal medicine and this statement is applicable to the etiology as well as the treatment of these conditions. In recent years the prevalence of rheumatic fever in the Armed Forces of World War II has lent special significance to this disease. The epidemics which have occurred in various training camps have afforded unusual opportunity for the study of various phases of rheumatic fever such as the role of the *Streptococcus hemolyticus*, prophylactic value of the sulfonamides, and the efficacy of intravenous salicylate therapy.

Rheumatoid arthritis has played a less important part in military life, but a goodly number of cases have come under observation at special hospitals for rheumatic disease such as the Army and Navy General Hospital at Hot Springs National Park, Arkansas. In civilian life arthritis continues to plague the practitioner because of the disappointing results obtained with treatment. It is true that the introduction of gold salts has brightened the picture considerably so far as rheumatoid arthritis is concerned. It is also true that sulfonamides and penicillin have simplified the treatment of gonorrheal arthritis. For osteoarthritis however we must still depend chiefly on rest, physiotherapy and salicylates.

A good deal of interest centers now on the clinical variants of rheumatoid arthritis such as arthritis psoriatica, Marie-Strümpell disease and Reiter's syndrome and there is more and more feeling that there exists some fundamental relationship between rheumatoid arthritis and such similar conditions as periarteritis nodosa, lupus erythematosus, dermatomyositis and scleroderma. The interesting experimental investigations of Rich and his co-workers may eventually lead to a better

understanding of the pathogenesis of all these mysterious conditions

As Sponsor for this issue of the *Medical Clinics*, I wish to extend my sincere thanks to the contributors who, in spite of many other pressing duties, have so kindly consented to write the articles which constitute this New York Number

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treatment of acute attacks sulfonamides proved of no value, indeed sulfonamides may aggravate the acute attacks^{55 75}

However, in contrast to their ineffectiveness in the *treatment* of acute attacks, sulfonamides appear to be definitely effective in the *prevention* of acute (recurring) attacks, a matter of very great importance. Most stimulating and encouraging have been the reports on the prophylactic use of sulfonamides in the treatment of (1) individual patients previously affected with acute rheumatic fever and of (2) large groups of persons, generally military personnel, susceptible to epidemics of streptococcal respiratory infections and their rheumatic sequelae (mass prophylaxis against rheumatic fever).

As a result of such studies, made during the last nine years, it now behooves every physician who sees a case of acute rheumatic fever to ask himself these questions: "When this acute attack is over, should I institute sulfonamide prophylaxis and continue it indefinitely? Would I be likely to harm the patient if I did institute it, or would I be harming him more if I didn't?" Similar questions are in order with reference to the rheumatic child or adult whose rheumatic fever is in a stage of apparent quiescence. Even though such patients are apparently "getting along all right," should the physician continue to let "fate" take care of matters or would sulfonamide prophylaxis provide a definitely superior and reasonably harmless form of protection against the (otherwise) almost inevitable recurrences?

For answers to these questions let us review the record.

1 Sulfonamides for the Prevention of Rheumatic Attacks, Prophylactic Treatment for Individual Rheumatic Patients.—The studies of Thomas and France,⁷⁸ begun in September, 1936, and of Coburn and Moore,¹⁵ begun about the same month, were reported simultaneously in January, 1939. To rheumatic patients whose disease was not "active" at the time, sulfanilamide was given in small doses daily throughout the fall and winter months when hemolytic streptococcal infections of the respiratory tract most commonly occur. The sulfanilamide appeared to exert a powerful prophylactic effect. Thereafter similar studies were conducted in several other American clinics. In the accompanying table we have summarized all the reports of this form of treatment so far published. The effects of sulfonamide prophylaxis have been observed for more than nine hundred "patient-seasons,"^{*} at nine separate institutions and in several different sections of the nation. The results among the patients "protected" by sulfanilamide were compared with the outcome among an almost equal number of patients to whom no sulfonamides were given. The comparison is striking.

* A "patient-season" here refers to the treatment of one patient over one fall and winter season. Hence "two patient-seasons" would refer to the treatment either of two patients during one fall and winter season, or of one patient over two fall and winter seasons.

SUMMARY OF CONSOLIDATED REPORTS ON SULFONAMIDE PROPHYLAXIS OF RHEUMATIC ATTACKS

Investigator	Year	Patients Treated		Untreated Controls		Toxic Reactions
		Person seasons	Rheumatic Attacks (Definite)	Person-seasons	Rheumatic Attacks (Definite)	
Thomas, Francis and Reichsmann ¹⁷⁻¹⁹	1939 1941 1942 1944	114	4	150	21	Rare generally mild
Coburn and Moore ¹⁵⁻¹⁷	1939 1940 1941	184	1	163 100	37 13	In 10%, generally mild
Stowell and Button ¹⁶	1941	46	0	14	2	In more than 30%, one fatal
Hansen Platon, Dwan and Pennoyer ^{20, 21}	1942 1944	131	7	58	27	Rare
Kanttner and Reyersbach ^{22, 23}	1943 1945	103	1	104	23	Had to stop treatment in 15%
Chandler and Tausug ²⁴	1943	41	0	41	5	Few mild
Dodge, Baldwin and Weber ²⁵	1943	170*	6	138	19	Mild and rare
Meeseloff and Robbins ²⁷	1943	50	3	60	3	Few mild
Feldt ²⁸	1944	89	0	42	3	Infrequent and unimportant
Anderson ¹⁸	1945	104	0	470	30	Occasional mild
Total		1 037	22 = 2.2%	1 340	183 = 13.7%	

* Dodge, Baldwin and Weber studied 181 person-seasons but eleven had already been reported by Kanttner and Reyersbach hence the latter are subtracted for this consolidated report.

Among the rheumatic patients protected by sulfonamides over 1,037 seasons only twenty-two acute rheumatic exacerbations occurred, an incidence of 2.2 per cent, and only three patients died from rheumatic fever. But among the rheumatic patients who received no sulfonamide during 1,340 seasons, there were 183 acute attacks (an incidence of 13.7 per cent) and five deaths from rheumatic fever. In other words among the rheumatic patients *not* given sulfonamide there were six times as many acute recurrences and almost twice as many deaths (to date) as among those who received sulfonamide prophylaxis.

Let us now analyze the details of the program.

Optimal Time to Begin Administration of Sulfonamides in Relation to Latest Attack—Because sulfonamides sometimes accentuate the symptoms of an acute attack, most investigators refrained from starting sulfonamide prophylaxis until four to six weeks after all signs of activity of the latest rheumatic attack had disappeared. Other physicians, caring for patients hospitalized during attacks, preferred to start the prophylactic doses of sulfonamide before the patient left the hospital, even though the disease was still slightly active. Thus the patient might be better protected against possible carriers of hemolytic streptococci in his home environment.⁶⁴

Time of Year for Sulfonamide Prophylaxis—To date practically all of the patients were treated only during the fall and winter months. But Dodge,⁶⁴ Kuttner⁶⁴ and Thomas⁷⁷ expressed the belief that it is a better plan to administer sulfonamide throughout the year, in order not only to minimize the likelihood of drug sensitivity which might result from interrupted dosage, but chiefly to provide more complete, year round protection.

Choice of Drug—To date sulfanilamide has been used in most cases, sulfathiazole or sulfadiazine in a few.³⁶ At a government conference attended by medical specialists sulfadiazine was considered preferable to sulfanilamide, and sulfamerazine was regarded as potentially the sulfonamide of choice. Since sulfamerazine is excreted slowly by the kidneys, it should be possible to maintain an effective blood level by giving one small daily dose.⁶⁴

Dosage—In general the daily dose was, for children, about 0.5 to 1 gm of the sulfonamide (generally sulfanilamide), for adults, 1 to 2 gm. To maintain an even saturation of the tissues the drugs were given at regularly spaced intervals, either three doses daily, each at eight hour intervals, or two doses daily, each twelve hours apart, for example, 7 A.M. and 7 P.M.

Blood Level—Occasional determinations of the level of sulfonamide in the serum or qualitative tests of the urine for sulfonamides were made to show whether patients were taking the drug. Most workers attempted to maintain a level of 1 to 3 mg per 100 cc of serum.

Follow-up Examinations—Careful instruction, regular follow-up

Theoretical considerations led certain investigators to fear that some patients, treated with small amounts of sulfonamides over long periods, might become "sensitive" to these drugs and later be unable to take them for other therapeutic purposes. However, no such sensitization was observed. It was also suggested that sulfonamide prophylaxis might produce periarteritis nodosa but no such reaction has been noted. Finally, there was some concern that virulent drug-fast strains of hemolytic streptococci might result from prolonged sulfonamide prophylaxis,^{45, 58} no such eventuality has been reported. Should such strains develop, penicillin would probably be effective against them.

Comment—This new and promising method for controlling rheumatic exacerbations appears to represent a really important medical advance. Its limited use to prevent recurrences among rheumatic soldiers has been approved,⁸² the drug of choice being 0.5 to 1.0 gm of sulfadiazine daily while the patient was under sufficient observation. Few exceptions can be taken to the conclusions which thus far have been drawn from the studies outlined in previous paragraphs. However, Wilson and Lubschez have stated their belief that many of the reported statistics are misleading. They have criticized especially the manner in which controls were chosen for some of the studies. According to them, the likelihood that a major exacerbation will occur depends not so much on such factors as the number of previous attacks, the severity of the disease and the particular year in which a given study was made as it does on the age of the patient and the length of time since the last attack, factors which, although more important, were not adequately considered in choosing controls for study. Having determined the rates of recurring attacks in their own cases, Wilson and Lubschez used these rates as "standards" and compared them with the rates in a number of the published studies on sulfonamide prophylaxis. In four of five reports thus examined, they found the observed number of recurrences among the sulfonamide-treated patients not significantly lower than the expected number. Consequently they expressed the belief that conclusions on the efficacy of chemoprophylaxis should not be drawn from these studies and that summations such as given in the table do not present a correct picture of the results.

In view of this controversy and to obtain the opinion of a medical statistician of wide experience we submitted to Dr. Joseph Berkson the data and opinions of Wilson and Lubschez and those of several proponents of sulfonamide prophylaxis. Berkson concluded that the value of sulfonamide prophylaxis had not been disproved by Wilson and Lubschez. Berkson objected to the fact that Wilson and Lubschez used as standards their own recurrence rates without checking them against those of other series to determine whether their "standards" were universally applicable. Berkson stated his belief that until such a comparison has been made there is no assurance that the rates cal-

culated by Wilson and Lubschez can be applied to other series. More over in each of the studies criticized by Wilson and Lubschez there was an *ad hoc* control group of untreated patients which was compared with the treated group. This method is generally recognized as experimentally more reliable than comparison with a "standard" obtained from a series observed at a different time and under different conditions. Statistical adjustment for the difference of age in the groups compared showed, if anything, a greater average difference of rates, favorable to the treated patients, than reported by the original authors.

Our Conclusions on Sulfonamide Prophylaxis for Rheumatic Patients—Although the exact value of sulfonamide prophylaxis for rheumatic fever appears still to be a matter for some debate for the present the arguments in favor of this procedure appear to be much stronger than those so far advanced against it.

The patient and his family may be put to some expense and trouble in the conduct of this treatment and there is a slight risk of toxicity from sulfonamides. But these disadvantages appear to be quite justified in the expectation of reducing materially the chances for acute exacerbations for prolonged invalidism or even for an early death from rheumatic carditis or from subacute bacterial endocarditis which eventualities so often occur when rheumatic fever is allowed to pursue its usual course.

On the basis of present knowledge we approve the use of sulfonamide prophylaxis for most rheumatic patients. But before any physician embarks on such a program or outlines his own scheme of treatment he should review the sixteen original references cited herein especially should be read the diversified opinions and plans outlined in the report of the Washington Conference of October, 1943.¹⁴

When sulfamerazine and other improved sulfonamides become widely available the chances of significant toxicity already small should be materially reduced. Then even more than now will the risks from the disease, treated otherwise, be obviously greater than those inherent in chemoprophylaxis. Approaching the ideal agent would, of course be a potent oral preparation of penicillin.

2 Mass Prophylaxis with Sulfonamides—During the past three years sulfonamides were administered to great numbers of persons in the armed services as a prophylactic measure against respiratory infections. An appreciation of the size of these experiences is obtained from reports such as those of Watson and his co-workers¹² who treated "several thousand" persons of Hodges who treated 10 000 persons of Holbrook who studied the course of 40 000 persons of Coburn,¹⁴ who studied 30 000 persons, and of Lee who reported studies on 25 000 persons.

Effectiveness of Mass Prophylaxis—The results of this work are only now being analyzed but preliminary reports indicate that the plan worked remarkably well.^{4, 12, 13, 14, 15, 16, 17, 18, 19, 20} All who made these studies

agreed that the incidences of hemolytic streptococcal respiratory infections, of scarlet fever, of meningococcal infections and of gonorrhea were greatly reduced. With regard to rheumatic fever, Carter, Coburn¹⁴ and Holbrook reported reductions paralleling those in the incidence of respiratory infections caused by the hemolytic streptococcus. Carter reported that at a certain post "the rate of admission for scarlet fever varied from 63.5 to 171.6 per 1,000, during the observation period before the use of sulfadiazine. Following the institution of prophylaxis the rate fell to zero within two weeks." The incidence of tonsillitis fell from 426 per 1,000 to 46 per 1,000 and the incidence of rheumatic fever was "reduced from 87 per 1,000 to zero within four weeks" after the program was begun.

Toxic Reactions Encountered during Mass Prophylaxis—The incidence of toxic reactions encountered during these large studies was low. Typical comments on these toxic reactions were those of Watson and co-workers,⁹² who stated that reactions were "few and mild," and of Hodges, who observed "no serious reactions to the drug." Holbrook stated that among 40,000 persons so treated only 0.12 per cent had any type of reaction and only thirteen persons (0.03 per cent) lost time from duty because of reactions, none of the reactions proved fatal. Coburn¹⁴ observed mild reactions (evanescent rashes) in only 0.5 per cent, "dangerous constitutional disturbances" (exfoliative dermatitis or granulocytopenia) occurred about once in every 10,000 persons receiving prophylaxis (incidence 0.01 per cent). Lee's rates of toxicity were very similar to those of Coburn: some reaction in 0.5 per cent, serious reactions in 0.036 per cent, no fatalities.

Conclusions Regarding Mass Prophylaxis for Respiratory Diseases and Rheumatic Attacks—Since sulfonamide prophylaxis apparently has proved effective in controlling the incidence of hemolytic streptococcal infections in large groups of persons who live in close contact, it should be expected to reduce also the incidence of rheumatic fever. The Surgeon General of the United States Army recently recommended the use of sulfonamide prophylaxis at the discretion of unit commanders when the incidence of hemolytic streptococcal infections among troops became high.^{83, 84}

These reports should engage the early attention of institutional physicians in attendance at schools, colleges and camps.

VACCINE PROPHYLAXIS OF RHEUMATIC ATTACKS

During the past twenty years, attempts have been made to reduce the incidence of rheumatic attacks by vaccination against streptococci.²⁰⁻⁹⁰ Results were not convincing and the procedure did not achieve widespread use. Since 1933, Wasson and Brown⁸⁷⁻⁹⁰ have been restudying the worth of vaccination. At first they used a crude hemolytic streptococcus toxin, more recently they attempted immunization

by a tannic acid precipitated toxin from the same streptococci. Their latest report concerned forty two patients immunized thus during 1941 none had rheumatic relapses, whereas, in a control series of thirty three patients, eleven suffered from attacks and three died. Among thirty-eight patients treated during 1942 only one suffered from a possible rheumatic recrudescence, while six rheumatic attacks occurred among forty nine untreated control patients.

These results are impressive and are about as good as those which have been claimed for sulfonamide prophylaxis. But until this work receives independent confirmation, no final opinion of its value can be formed.

USE OF A SALICYLATE TO PREVENT RECURRING ATTACKS

For many years physicians have attempted to lessen the number of rheumatic recurrences by the use of a salicylate given between attacks. Some physicians⁵¹⁻⁵³ gave small doses daily for several months others⁵ gave a salicylate one week of each month. But little evidence has been obtained to indicate that salicylates thus given, prevent rheumatic relapses. A different program of salicylate prophylaxis was recommended in 1938 by Schlesinger, who gave acetylsalicylic acid to rheumatic children as soon as an infection of the upper part of the respiratory tract developed and continued its administration until three or four weeks after the infection had subsided. He expressed the belief that the number of relapses and the mortality rate were definitely reduced. Among twenty seven patients given acetylsalicylic acid thus twenty-one recovered and six died, the mortality rate was 22 per cent. Among twenty four patients not so treated thirteen recovered and eleven died the mortality rate was 46 per cent.

A somewhat similar plan has been advocated recently by Coburn and Moore.¹⁸ Four to six grams of sodium salicylate were administered daily depending on the size of the patient. Administration of the drug was started as soon as acute pharyngitis appeared. If throat cultures revealed hemolytic streptococci, salicylates were continued for four weeks otherwise, administration of the drug was stopped. Of forty-seven rheumatic patients having hemolytic streptococcal pharyngitis so treated, only one (2 per cent) developed rheumatic fever. Among 139 untreated controls fifty seven (41 per cent) developed rheumatic fever. The number of patients treated in this manner is small. The work must be extended before it can be properly evaluated. With this plan, salicylates are given at a time when sulfonamides are powerless to prevent recurrences—that is between the onset of the acute hemolytic streptococcal infection and the usual time for the appearance of the rheumatic attack.³⁷ If therefore the claims of Schlesinger and of Coburn and Moore can be confirmed this method may prove to be a needed supplement to sulfonamide prophylaxis.

PREVENTION OF ATTACKS BY DIET

Although rheumatic fever affects the underprivileged, the poorly fed and the poverty stricken somewhat more often than those in better circumstances, repeated attempts have failed to prove that rheumatic fever is directly related to vitamin deficiency or to some other form of malnutrition. But after studying the dietary habits of rheumatic and nonrheumatic children, Coburn and Moore¹⁹ recently concluded that some correlation exists between the incidence of rheumatic attacks and the daily intake of protein. The patients susceptible to rheumatic attacks usually omitted from their diet eggs, rich in so many essential factors. To the daily diet of a group of susceptible rheumatic children Coburn and Moore added two eggs boiled five minutes and two frozen egg yolks. Most of these rheumatic children had been under clinical observation for years whenever hemolytic streptococcal infections had developed, at least 50 per cent of those so affected developed rheumatic attacks. But following the addition of the dietary supplements, none of twenty-four children with *quiescent* rheumatism who contracted infections of the respiratory tract with hemolytic streptococci developed acute rheumatic attacks. Children who had "active rheumatism" seemed unaffected by the addition of eggs to the diets.

This work must also be confirmed before the suggested plan can be properly evaluated.

PREVENTION OF RHEUMATIC ATTACKS BY CONTROLLING AIR BORNE TRANSMISSION OF HEMOLYTIC STREPTOCOCCI

Studies conducted during the war years demonstrated that infectious organisms may be suspended in the air, caught in small droplets of moisture or attached to particles of dust, and are still capable of transmitting infections after being transported by air currents for considerable distances ^{21, 39 43, 96, 97}

Since hemolytic streptococci are among the organisms transmitted in this manner, the subject of air-borne infections is of importance in considering measures to control rheumatic fever.

Experimental technics which have been developed to aid in the prevention of air-borne transmission have included the following (1) segregation or quarantine of persons who have hemolytic streptococcal infections, (2) the use of physical barriers such as face masks, filters, cubicles and partitions in rooms, (3) the application of oil to floors and bedding to reduce the volume of dust, (4) disinfection of air through use of germicidal vapors and (5) disinfection of air by ultra-violet irradiation.

1 Segregation or Quarantine—Because persons who have hemolytic streptococcal infections of the upper part of the respiratory tract can infect the air around them, such persons should be temporarily segregated or at least prevented from coming in contact with persons

susceptible to rheumatic fever. At present it appears impossible to segregate or quarantine all persons who have such respiratory infections. But an attempt should be made to apply this knowledge for the benefit of persons susceptible to rheumatic fever in schools, hospitals, convalescent homes and army posts. To the extent that segregation is possible, persons suffering from hemolytic streptococcal infections should be kept from infecting others especially those previously affected by rheumatic fever. Segregation should certainly be applied within the family unit.

2. Physical Barriers against Air Borne Infections—A study of the use of physical barriers at a nursery⁶⁰ showed that masks, cubicles and positive-pressure ventilating systems are capable of reducing somewhat the spread of air borne infections. However, these measures alone were not as successful as when combined with ultraviolet irradiation.

We believe that physical barriers should be used in hospitals and homes where persons susceptible to rheumatic fever are in close proximity to persons having hemolytic streptococcal infections of the respiratory tract.

3 Oiling of Floors and Bedding—It has been shown that dust in bedclothes and on floors in the vicinity of persons suffering from hemolytic streptococcal infections may act as a reservoir for these organisms.^{1, 31} If this dust is agitated and redispersed infection may spread to other persons in the room. To lessen the infectivity of barracks and hospital wards Robertson and his co workers^{58, 67, 68} of the "Commission on Air Borne Infections" developed certain practical measures: the oiling of floors and bedclothes and the use of sweeping with a moist broom.

Floors were oiled by applying a single coat of paraffin oil. Care was taken to sweep with moistened or oiled brooms. Blankets and bedclothes were oiled by using emulsions of water and oil as a final rinse in the process of laundering.⁴¹

4 Germicidal Aerosols.—Appreciation of the importance of air borne infections has revived interest in germicidal mists and vapors. This mode of sterilization first proposed by Lister, has been reinvestigated during the past few years at army installations and in certain civilian hospitals.^{9, 65} At present, propylene glycol and triethylene glycol appear to be the most satisfactory chemical agents for this purpose.^{35, 40} A simple apparatus has been devised which is capable of producing a nonirritant germicidal atmosphere in large rooms at a low cost. When such an apparatus was used a significant lowering of the incidence of respiratory infections was observed in hospital and nursery wards.

A similar apparatus for use in individual homes is in process of development. Robertson has expressed the belief that with it children susceptible to rheumatic fever may be given added protection against

hemolytic streptococcal infections spread from other members of a household

5 Ultraviolet Irradiation.—Ultraviolet lamps which provide constant protection regardless of climatic factors are capable of reducing atmospheric contamination and, by aiding in the control of air borne hemolytic streptococcal infections, they may be capable of reducing the incidence of rheumatic fever in persons living in irradiated places^{23, 24}

PROPHYLAXIS OF RHEUMATIC ATTACKS BY CLIMATE

Physicians are often asked their opinion as to the advisability of a change of climate for patients who have rheumatic fever To answer this question intelligently one must appraise available information concerning the incidence of rheumatic fever in various parts of the country and the effect of transporting rheumatic patients to supposedly safer climates

Most students of this subject have agreed that acute attacks of rheumatic fever are less frequently encountered in subtropical climates than in more temperate zones But this observation applies only to the acute, so-called exudative phase of the disease The incidence of the chronic proliferative stigmas of rheumatic fever has been found the same wherever the disease has been studied in this country Sites of especially high incidence of acute rheumatic fever are New England, the states along the east central seaboard, the Great Lakes region,^{59 61} south central Canada²⁸ and the Rocky Mountain region, particularly Colorado, where rheumatic fever was observed in epidemic form among troops A low incidence of acute rheumatic fever is found in southern California and the states bordering on the Gulf of Mexico

One might suppose that some advantage might result were susceptible persons transported from areas of high incidence to areas of low incidence But the results of such transportation have been difficult to evaluate⁶¹ Observations to date have been on a small scale The problem has not yet been studied thoroughly

There appears to be no merit in any particular "climate" per se, it is a question of whether or not, or to what extent, hemolytic streptococcal infections are prevalent If a change of residence can be accomplished without a destructive effect on home life or the family economics, on careers or on schooling, perhaps it is advisable in selected cases in which the whole family can readily be moved or in which the affected person is of an age and temperament to accept the transfer without feeling exiled, for, to be truly effective, the transfer should be essentially permanent A stay of mere weeks or months confers no immunity, the transferee merely escapes the provocative infection as long as he remains in the preferred locality

It is to be hoped that chemoprophylaxis will endow rheumatic persons with the ability to fight their battles successfully in their home

over oral administration except for persons prevented by nausea and vomiting from taking the drug by mouth. No differences were noted in the time necessary for articular pains to disappear or for the sedimentation rates to return to normal, in the incidence of polycyclic attacks or in the tendency of pre-existing cardiac damage to progress.^{93, 94} One group of investigators⁸⁶ reported that patients treated intravenously became afebrile sooner than those treated by the oral route but in no other respect was the intravenous method of advantage.

The intravenous administration of large doses of salicylates is not without danger. Several notable toxic reactions have been reported: hyperventilation, tetany and carpopedal spasm from disturbances of acid-base balance, stupor, unconsciousness or maniacal delirium.^{22, 26, 27, 80, 93, 94} Two deaths from disseminated hemorrhages have occurred that were ascribed to such treatment² but the hemorrhages may have been related to the disease and not to its treatment.

In our opinion, salicylates should be administered orally to patients who have rheumatic fever, except to those who cannot take the drug thus because of gastro-intestinal intolerance. In such cases, one may administer the drug intravenously or rectally. To be fully effective salicylates generally have to be given in amounts large enough to induce the early symptom of toxicity, mild ringing of the ears. Administration of such amounts should be continued until fever and articular inflammation have disappeared. If fever or arthritis recurs following withdrawal of salicylates, the drug should be given again until its withdrawal is not followed by such recurrence.

We do not believe that patients with rheumatic fever, given salicylates orally, are being denied a superior, more scientific form of therapy.

THE HEMORRHAGIC EFFECT OF SALICYLATES

Hemorrhagic visceral and cerebral lesions have been noted in cases of fatal salicylate poisoning.^{2, 26, 80} Occasionally patients with acute rheumatic fever have exhibited hemorrhagic symptoms, such as purpura, while being treated with salicylates. When it was discovered that dicumarol, the hemorrhagic principle of sweet clover, produces salicylic acid as one of its end products within the body,^{52, 73} it was suggested that salicylates per se may provoke hemorrhagic phenomena. Studies conducted to test this hypothesis may be summarized as follows. Sodium salicylate administered in amounts comparable to the doses used in the treatment of rheumatic fever does lower the prothrombin content of the blood,^{26, 58, 66, 71, 72} but only slightly.¹⁰ Hence the danger of hemorrhage from this effect is probably insignificant and the occasional hemorrhagic phenomena observed during acute rheumatic fever are probably symptoms of the disease rather than the effects of salicylates. The risk from hemorrhage during ordinary salicylate therapy need not be seriously considered unless a surgical

procedure is necessary during salicylate treatment. Patients requiring surgical treatment can be protected from undue risk of hemorrhage by the administration of vitamin K before and after the surgical operation.

TREATMENT OF ACUTE RHEUMATIC FEVER WITH PENICILLIN

Penicillin is ineffective in the treatment of acute rheumatic fever.^{80 85 91} But penicillin may be very useful in the treatment of acute streptococcal complications (Sulfonamides should not be used under such circumstances as they may aggravate the rheumatic fever). Twiss recently reported the successful treatment with penicillin of acute otitis media and mastoiditis in one case of rheumatic fever and of acute hemolytic streptococcal otitis media in another.

When a truly potent, relatively inexpensive oral preparation of penicillin⁸⁴ becomes available for wide use, the chemoprophylaxis of rheumatic fever by such a preparation can be expected to do much to reduce the incidence of acute rheumatic exacerbations by controlling the provocative hemolytic streptococcal infections.

THE NEED FOR CONSERVATISM IN EMPLOYING REST IN THE TREATMENT OF RHEUMATIC FEVER

There is a growing appreciation of the fact that the heart of the victim of rheumatic fever is damaged as time passes not particularly by ordinary physical activity but by the progressive inflammation of the rheumatic process itself, the underlying inflammation being aggravated from time to time chiefly by provocative infections. In the past, patients who had rheumatic fever have too often been overly protected from physical activity; too much rest has often produced mental and physical invalidism.

To avoid this needless complication in rheumatic soldiers the War Department warned medical officers not to overdo in the matter of resting convalescent rheumatic soldiers but to encourage them to resume graduated physical activity as soon as possible when evidences of active disease have subsided.

The War Department's memorandum⁸² in this regard may be instructive to civilian physicians. It reads thus:

Physical Activity after Recovery—The patient who has made a satisfactory recovery from rheumatic fever can be assured once he is physically fit, that limitation of physical activity is not helpful in protecting against additional attacks of subsequent heart disease and therefore is not indicated. It is important that this be made clear because the concept is so widely held that limitation of activity is essential in any condition which has any relation to cardiac injury.

Limitation of activity is so important in the causation of physical invalidism that such restrictions should not be prescribed especially for young individuals unless the indications therefor are unquestioned. Even in a large proportion of individuals with residual cardiac lesions of rheumatic origin, moderate physical exercise is beneficial rather than harmful. Whether or not crippling heart disease results from rheumatic fever as a rule depends on whether repeated attacks occur

CONCLUSIONS

1 Sulfonamide prophylaxis appears to represent a notable advance in the control of rheumatic fever and is recommended for persons who have had this disease

2 Prophylaxis with streptococcal vaccine is of uncertain value and cannot be recommended at present

3 Salicylates administered to susceptible persons at the onset of a hemolytic streptococcal infection have reportedly reduced the incidence of rheumatic attacks This procedure has not been sufficiently studied but appears worthy of further trial

4 Dietary supplements of certain foods and vitamins may aid in maintaining general good health but are as yet of uncertain value in preventing initial or recurring attacks of rheumatic fever

5 The control of air-borne hemolytic streptococcal infections by measures such as segregation, mechanical barriers, oiling of floors and bedding, vaporization of bactericidal chemicals and the use of ultra violet irradiation may be employed as additional aids in the prevention of rheumatic fever in schools, hospitals, convalescent homes and army barracks Physicians associated with such institutions should familiarize themselves with the merits of these procedures

6 The change of residence of the rheumatic patient to a geographical zone where the incidence of hemolytic streptococcal infections is low may be a worth-while procedure under exceptional circumstances

7 The treatment of acute rheumatic fever by salicylates administered intravenously offers no significant advantages except for patients whose gastro-intestinal intolerance interferes with the oral or rectal administration of the drug

8 The hemorrhagic effect of salicylates appears to be of little clinical importance

9 Penicillin is ineffective in the treatment of acute rheumatic fever but is recommended for the treatment of streptococcal complications of this disease

10 The conservative employment of rest in the treatment of rheumatic fever is recommended

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THE HEART IN RHEUMATIC FEVER

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IN a consideration of the effects of rheumatic fever on the heart, we have to take into account (1) the acute involvement of the heart, and (2) the chronic stage of rheumatic heart disease I shall attempt in this paper to give a kaleidoscopic view of the consequences of rheumatic infection of the heart

ACUTE RHEUMATIC HEART DISEASE

The causative agent of rheumatic infection may involve the myocardium, the endocardium or the pericardium in any combinations or all of these may be involved The usual picture is for the subject to have an acute tonsillitis and two weeks or so later there is migratory polyarteritis, rise in temperature, and the clinical picture recognized as acute rheumatic fever

In a patient who has acute rheumatic fever, how do we recognize involvements of the various parts of the heart? The *endocardial involvement* is a valvulitis and is recognized by appropriate murmurs Early a systolic murmur may appear at the apex or over the base indicating mitral insufficiency and aortic roughening respectively As time goes on, a diastolic murmur may appear at the base and also at the apex Systolic murmurs may be related to fever or to anemia should it occur, and may disappear, but diastolic murmurs are usually more grave in their import, indicating the occurrence of aortic insufficiency or mitral stenosis The progression of these lesions will be discussed later The Aschoff body is the pathological evidence of *myocardial involvement* When the myocardial involvement is extensive, there may be gallop rhythm, sinus irregularity disappears, the heart may increase in size and heart failure may rapidly appear Myocardial damage is detected objectively by the occurrence of T-wave alterations in the electrocardiogram All varieties of irregularities of cardiac rhythm may be encountered premature contractions arising from the auricles, or auriculoventricular system or from the ventricles, auricular fibrillation and flutter, paroxysmal tachycardia from the auricles or auriculoventricular system or the ventricles And finally any grade of damage to the conducting system may occur in that the P-R time may be prolonged slightly, there may be marked prolongation with occasional blocked P-waves or Wenckebach's phenomenon

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may appear, or there may be 2 1, 3 2 etc. heart block and complete heart block. During the observation of a patient with acute rheumatic fever, the onset of halving of the heart rate should suggest 2 1 heart block clinically. Occasionally there may be bundle branch block. The rapid onset of shortness of breath, increase in heart rate, dyspnea and cyanosis, filling up of the neck veins and gallop rhythm are evidence of acute heart failure due to the damaged myocardium. There may be precordial distress in the absence of pericarditis. The conduction changes have been related to the involvement of the conducting system, presumably by the Aschoff lesions and more recently have been attributed to vagus effects¹

The interpretation of T-wave changes requires care because marked alterations may occur during the acute stage of tonsillitis before and without the onset of rheumatic fever

When *pericardial involvement* occurs, the patient usually becomes much more ill. There is precordial distress or pain, respirations become hurried and shallow. A to-and-fro pericardial friction rub is heard synchronous with the heart beat. It may be localized over a small area or widespread. It may be confused with or mistaken for systolic and diastolic murmurs. The rub may be transient or persistent. It may disappear and be without further consequence or its disappearance may indicate the formation of pericardial effusion. If the fluid accumulates rapidly serious cardiac embarrassment occurs due to the tamponade of the heart. The respirations become more shallow, the blood pressure falls, and the pulse becomes paradoxical in type. The percussion outlines of the heart increase in size, the point of maximal impulse disappears, the heart sounds become more distant, tachycardia increases, the neck veins become more distended, the circulation time becomes prolonged and the venous pressure elevated². The liver may become tender due to rapid stretching. There may be compression of the lung posteriorly at the angle of the left scapula giving signs of consolidation. In typical instances, the T-waves of the electrocardiogram go through alterations characteristic of pericardial involvement. Early, there is elevation of the R-T segments in all leads followed by coving of the T-waves which may persist for many months. The fluid may be absorbed or the compression of the heart may become so hazardous as to require pericardial tap to relieve the tamponade. In the course of acute rheumatic carditis, it is important to separate the picture of cardiac dilatation and failure from the almost similar picture of pericarditis with effusion, because different therapy is indicated in each. Pericarditis with effusion may be completely absorbed without residua or there may be tags of adhesions or the pericardial cavity may be obliterated and dense adhesions bind the heart to the anterior chest wall—in short, adhesive pericarditis may take place. When this occurs it does not give the picture of Pick's disease or so-called chronic constrictive pericarditis^{3, 4}.

Heart failure in acute rheumatic fever is usually due to the myocardial involvement and not to the valvular involvement, with this exception. If the patient has had rheumatic fever before and has valvular disease or deformity already, the onset of another episode of acute rheumatic fever may precipitate heart failure in a heart which is able to maintain compensation until the strain of the infection is added.

What are the Essentials of Treatment for These Various Complications in the Acute Stage of Rheumatic Fever?—Experience has shown that neither penicillin^{5, 6} nor sulfa drugs⁷ are of benefit in the treatment of acute rheumatic fever after its onset. They do not prevent the cardiac complications nor are they helpful in the treatment of them when they arise.

Salicylates have been used in the treatment of acute rheumatic fever in the past with the general notion that they rapidly alleviated the joint manifestations, lowered the temperature but that the other manifestations of rheumatic infection ran their course and for the most part the duration of the infection was not shortened by their use. The effect of salicylates on joints and temperature has been so constant and dramatic that they have been used diagnostically in less clear-cut instances of joint involvement in which the diagnostic rubric was not clear. It was the opinion that the drugs had no effect on the prevention or cure of the cardiac complications.^{8, 9, 10}

Recently, Coburn¹¹ has advocated the use of *massive doses* of salicylates, on the average of 10 gm per day, with the notion of maintenance of a blood level of 35 mg per per 100 cc or higher. It appears that the use of salicylates intravenously has no advantages therapeutically over the oral administration.¹² The results of the use of massive doses are not conclusive. Some report shortening of the course^{11, 13} and restoration of the sedimentation rate to normal,¹³ others that the course of the rheumatic infection is not shortened,¹⁴ that the sedimentation rate does not promptly return to normal levels,^{12, 15} and that pericarditis has appeared when adequate blood levels of salicylates were being maintained by intravenous use of the drug,¹² as well as the development of persistent valvular lesions (quoted by Wright¹²). Boas and Ellenberg¹⁶ thought that massive doses of the drug brought about prompt relief from pericarditis with effusion, but had no effect on the endocarditis or myocarditis.

The use of massive doses of salicylates has led to instances of salicylate intoxication and death.^{17, 18} No doubt there are many instances which have not been reported. In addition to the more or less mild symptoms which were formerly used to warn about its use, namely tinnitus, nausea and vomiting, with the larger amounts there is hyperventilation and alkalosis and sometimes nephritis or liver damage resulting in lowered prothrombin. The use of sodium bicarbonate with each dose of salicylate will frequently prevent the alkalosis (Wright¹²; from Coombs) but will lower the salicylate level of the blood.¹⁹

Moderate or larger doses of sodium salicylates induce hypoprothrombinemia which may regress as treatment progresses^{17 20 21 22} Large doses of vitamin K appear to prevent the development of the prothrombin deficiency and hasten restoration to normal levels when it has occurred.¹⁷

As the matter stands for the moment it is not clearly demonstrated that massive doses of salicylates cure rheumatic infection or prevent the complications. If large doses are used care should be exercised to detect early salicylism. Adequate doses of the drug should be used to bring down the fever and alleviate the joint symptoms, out of this has been demonstrated that blood levels should be estimated when the drug is given.²³ The pendulum having swung far over to massive doses will probably swing back somewhere in between smaller amounts which were used formerly and the large amounts recently advocated.

Heart Failure—The occurrence of heart failure is treated as in other instances of heart failure. (1) The patient is in bed propped up as comfort dictates. (2) The daily fluid intake is reduced to 1200 to 1500 cc. (3) A 2 to 3 gm. salt diet is given. (4) The oxygen tent or mask may be very useful. (5) The patient is digitalized. 18 gm. of digitalis leaf such as that distributed by the New York Heart Association may be given by mouth in twenty four hours if the patient has not had digitalis beforehand.²⁴ This may be given as follows: 0.8 gm. at once followed in four hours by 0.5 gm. more, in four hours by 0.3 gm. more and four hours later still by 0.2 gm. The successive doses are not given if nausea or vomiting occurs or the heart rate falls below 70 per minute. If there is urgency, digitaline nativele may be given in dosage of 1.2 mg. by mouth or intravenously to start digitalization. Doses near 18 to 20 mg. appear to be in the range of the amount required for adequate digitalization. Experience has shown that digitalis may be given when required in acute rheumatic fever even in the presence of conduction defects.²⁵ In my experience, children require approximately the same dosage as adults for adequate digitalization irrespective of body weight. (6) Mercupurin or salyrgan theophylline 2 cc. intravenously may be required at three-day intervals. (7) Ammonium chloride may be used to enhance the effect of the mercurial diuretics.

Pericarditis—The early use of the ice bag and sedatives (codeine) may be palliative. When effusion occurs the question arises about pericardial tap. Boas and Ellenberg¹⁶ found that the use of massive doses of salicylates bring about rapid absorption of the pericardial fluid. If fluid is accumulating rapidly and compression of the heart is extreme, a pericardial tap may have to be resorted to but should be done slowly in order not to allow the heart to expand rapidly. In the presence of pericarditis with effusion it is best not to use digitalis. Digitalis makes the heart smaller^{26 27 28} and it does not appear wise to further decrease in size a heart which is already compressed so that it cannot relax to admit blood into its chambers.

Mobilization after Rheumatic Infection—Patients should remain in bed until all evidences of rheumatic activity have disappeared. The patient should be observed without salicylates before mobilization is started, to see whether there will be recurrence of symptoms or signs of infection. Absence of tachycardia and of fever, return of sedimentation rate to normal, normal white blood cell count, stabilization of the electrocardiogram, absence of evidence of cardiac insufficiency, and the general well-being of the patient are used as guides. The speed of mobilization depends on the duration of the stay in bed, the severity of the disease and what complications had been encountered. In general, fairly strict rest should be enforced for at least one month after the last sign of activity has disappeared. How much activity is finally achieved depends for the most part on the status of the heart.

CHRONOLOGICAL EVENTS

The patient may have rheumatic involvement of the various parts of the heart and recover without any cardiac damage being left. Commonly there is valvular damage and less rarely there is adhesive pericarditis. The more frequent the recurrences, the more cardiac damage is to be expected.

Recurrence.—Young patients are more likely to have recurrence of rheumatic activity each year, but the longer a patient goes without recurrence activity, the better the chances are of escaping further rheumatic infection. Recurrences are more common in adolescents. Rheumatic fever occurs in girls twice as often as in boys.

Valve Damage.—From the onset of infection until the establishment of rheumatic heart disease requires months to years. The changes that go on in a mitral valve leading to stenosis, for instance, require months to years for their evolution and the establishment of clinical mitral stenosis. It is recalled that in only about 50 per cent of the cases of rheumatic heart disease is a history of rheumatic infection obtained. With recurrence there may or may not be increase in the increment of valvular damage or additional lesions may be added. Mitral involvement alone is the most common lesion, next mitral and aortic combined, much less frequently aortic alone and less frequently tricuspid involvement. The statistical data relating to rheumatic fever and rheumatic heart disease are recorded in the recent papers of Cohn and Lingg,^{29, 30} which serve as excellent reference source.

Rheumatic infection leads to valvular damage that may present the diagnosis of mitral insufficiency, of mitral stenosis and insufficiency, of aortic insufficiency, of aortic stenosis and insufficiency (rarely to aortic stenosis alone), to mitral stenosis and insufficiency and aortic insufficiency, or mitral insufficiency, mitral stenosis, aortic stenosis and aortic insufficiency, and to these may then be added tricuspid stenosis and insufficiency. Smith and Levine³¹ and Cooke and White³² have shown that the more frequently tricuspid stenosis is sought for

on clinical examination the more frequently it will be found, and in a patient with mitral stenosis, mitral insufficiency, aortic stenosis and aortic insufficiency, there is a fair chance that tricuspid stenosis and tricuspid insufficiency are also present. Smith and Levine³¹ found that the average age at death is less in the presence of tricuspid stenosis, but the duration of failure was longer. It is recalled that tricuspid insufficiency may occur during heart failure.

The natural history of the disease in the patients with each of these valve defects differs in the broad features. A patient may have mitral stenosis for many years and maintain a small heart and remain without symptoms. A patient with mitral stenosis begins to have symptoms sooner than a patient with aortic insufficiency and will respond satisfactorily to treatment and go on for years. On the other hand, the patient with aortic insufficiency goes on for years with no limitation of his functional capacity. I recall one patient with aortic insufficiency and a tremendously enlarged heart who was a Golden Gloves boxer. However, when the patient with aortic insufficiency begins to have symptoms and failure, the downhill course is more rapid and progressive. Patients with tricuspid stenosis and insufficiency and mitral stenosis and mitral insufficiency may do better after the onset of failure than those patients without the tricuspid stenosis. The stenosed tricuspid ring prevents the delivery to the heart of more blood than the stenosed mitral ring can conduct through its orifice.³² Such patients have a preponderance of ascites and hepatic enlargement.

Functional Capacity—Stewart and his associates have studied the functional capacity of patients exhibiting various valvular defects of rheumatic etiology. These patients had never suffered from congestive heart failure.^{33, 34} The average cardiac index (cardiac output in liters per minute per square meter of body surface) was decreased. The arteriovenous oxygen difference was increased. The stroke volume was decreased. The venous pressure and circulation time were within the normal range. The order of magnitude of the functional defect increased progressively in going from the mitral stenosis, mitral insufficiency, aortic insufficiency group to the mitral stenosis, mitral insufficiency group to the mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency group. The functional capacity of mitral stenosis and mitral insufficiency was improved by the addition of aortic insufficiency, which may be due to dilatation of the mitral ring by the aortic lesion increasing the size of the left ventricle. It may be recalled that Levine³⁵ thought that hypertension served the same purpose. A group of patients exhibiting mitral stenosis before the onset of failure was compared with a group during failure and again after the restoration of compensation. It was found that during failure the arteriovenous oxygen difference increased further, the cardiac index decreased further, the circulation time became longer and the venous pressure rose, and the work of the heart was no longer commensurate with its

size With the recovery from heart failure the functional capacity increased but usually did not regain its prefailure level^{33 34}

WHAT ARE THE HAZARDS TO WHICH A PATIENT WITH RHEUMATIC HEART DISEASE IS SUBJECT?

1 The heart may not increase in size early but usually *enlarges* and maintains an adequate circulation until the patient puts it to too great a demand, or until recurrence of rheumatic infection or an attack of respiratory acute infection or bronchitis put an increased burden on the heart

2 The rhythm may remain normal or change to *auricular fibrillation* This is common in patients with mitral stenosis and less common in those with pure aortic involvement. Onset of auricular fibrillation may or may not precipitate heart failure De la Chapelle, Graef and Rottino³⁶ and De Graff and Lingg³⁷ have shown that auricular fibrillation is not in itself of ill omen, but that it was a late complication, coming on toward the end of the natural course of the disease Two and one-half years was the average life span after the onset of auricular fibrillation, but many patients survive its onset for many, many years

When normal rhythm is replaced by auricular fibrillation the question of the use of quinidine arises in order to attempt to restore regular sinus mechanism Restoration of normal rhythm should not be attempted (a) if the heart is very large, (b) if fibrillation has been present for a long time, (c) if heart failure is present, and (d) usually if the patient has ever had heart failure Mural thrombi are likely to form under the above conditions and from them emboli may arise on assumption of coordinated contraction of the auricles If the patient after due consideration is thought to be a suitable candidate for the use of quinidine the ventricular rate should be slowed first with digitalis in the usual way Reversion to normal rhythm may occur during this period. This drug is then stopped and a test dose of 0.2 gm quinidine is given²⁴ Four hours later 0.4 gm of the drug may be given, and may be repeated at four-hour intervals until a dosage of 1.6 gm to a maximum of 2 gm is given a day If reversion does not occur after two or three days the drug is discontinued and the ventricular rate again slowed with digitalis Another attempt may be made if there have been no toxic effects During the use of quinidine the heart rhythm is observed for ventricular premature contractions and the QRS time in the electrocardiogram measured to detect an increase If restoration of normal rhythm takes place, 0.2 gm of quinidine may be given twice a day for a week or ten days to prevent recurrence of fibrillation The patient should be in bed during attempts at reversion In the treatment of paroxysmal auricular fibrillation after the first restoration to normal with quinidine patients may be instructed to take quinidine at the onset of irregularity

3 *Heart failure* may occur in the presence of normal rhythm or of auricular fibrillation. It may have been of gradually progressive onset with gradual increase in dyspnea and limitation of activities until varying degree of failure occurred. On the other hand, failure may have been precipitated by the onset of auricular fibrillation or of auricular flutter or auricular paroxysmal tachycardia, or of an acute exhibition of more work than the patient was accustomed to do, or onset of hyperthyroidism, during pregnancy or the increased demands of labor, acute respiratory infection or acute bronchitis.

4. Patients with chronic heart disease may have *premature contractions* or *paroxysmal tachycardia* from auricles, auriculoventricular node, and less commonly from ventricles, or auricular flutter. Bouts of auricular premature contractions may precede the onset of auricular fibrillation or auricular paroxysmal tachycardia.

5 Patients with mitral stenosis and especially when auricular fibrillation is present may have *mural thrombi* which give rise to emboli and infarction. Infarction of the lungs, brain, kidneys, spleen, and closure of the arteries of the legs and mesentery occur and give rise to appropriate signs and symptoms.

6 Patients with aortic stenosis are subject to *fainting attacks*, the cause of which is conjectural.³⁸

7 Rheumatic fever is the basis of the so-called "calcific aortic stenosis" found in older individuals in a large percentage of the cases.³⁹

8 The most dreaded complication of rheumatic heart disease was formerly held to be *subacute bacterial endocarditis*, it occurred in about 4 per cent of the cases. It has been the common experience that it occurred rarely after the onset of auricular fibrillation.³⁷ It is most commonly found on the mitral and the aortic lesions. With the institution of penicillin therapy recovery from this complication is common.^{40, 41, 42} The incidence of subacute bacterial endocarditis in cases of luetic heart disease is rare and in many of these there may be a rheumatic background in a patient who also had luetic heart disease.⁴³ After recovery from subacute bacterial endocarditis the valvular defects remain. Zeman⁴⁴ has recently reemphasized the high incidence of rheumatic valvular lesions as the basis for the endocarditis with the occurrence in this role less frequently of arteriosclerotic and syphilitic heart disease. Gross⁴⁵ and Koletsky⁴⁶ have pointed out the role of rheumatic infection in the so-called "bicuspid aortic valves," showing that most bicuspid valves in adults are acquired lesions produced by rheumatic fever.

9 Among the most common accidents which patients with mitral stenosis suffer are episodes of *pulmonary hemorrhage*.⁴⁷ These are due to increase in pressure in the pulmonary circuit because of the obstruction by the narrow mitral ring. Patients may exhibit this as the sole evidence of heart failure for many years. They may expectorate only a small amount of blood or have profuse hemorrhage. Many

of these patients are erroneously thought to have pulmonary tuberculosis and find their way to tuberculosis clinics rather than the cardiac clinics. Ferguson, Kobilak and Deitrick⁴⁸ have recently tried to locate the source of bleeding in mitral stenosis

TREATMENT OF PATIENTS WITH RHEUMATIC HEART DISEASE

1 The treatment of acute episodes of failure and pericarditis has been described

2 A patient who has recovered from an attack of rheumatic fever without cardiac involvement may lead a normal life, with adequate sleep, rest, care of teeth and colds and respiratory infections

3 *Care of patients with chronic rheumatic heart disease before the onset of failure* In my experience these patients do best under limited activities even though subjectively they have no symptoms. I recommend that they always stay below what they are able to do comfortably. They should do everything slowly. Briefly the advice is as follows: Not to walk stairs when elevators are available, to go slowly on hills, bathe in warm water, may swim in quiet water, but never get in a situation where they have to push themselves and cannot stop when they wish, care of cold and respiratory infections—remain at home in bed for a day or so, watch for recurrence of evidence of rheumatic activity ten days to two weeks after sore throat or cold, regular vacations, select a job which is compatible with their functional capacity. Their physicians should be consulted about the advisability of pregnancy. The object is to train the patient to try to prevent onset of failure.

4 *Treatment of patients during heart failure* With the onset of failure I prefer to treat the patient in bed rather than ambulatory, first restoring compensation and then increasing his activities up to what he is capable of. The essentials are the same as used in treating the acute heart failure: (a) Remain in bed, (b) fluid intake limited to 1200 cc per day, (c) 2 gm salt, high protein* diet, (d) digitalization as described under acute heart failure. In the presence of auricular fibrillation the ventricular rate is an excellent guide to adequate therapy. (e) The use of quinidine has already been considered but is contraindicated in heart failure. (f) Mercupurin or salyrgan-theophylline 2 cc intravenously every third day may be required. I do not think it wise to give the drug more frequently and the use of small daily injections is not satisfactory. (g) Ammonium chloride, 1 gm. three times a day, may be used to enhance the effect of the mercurial diuretic. (h) Urea, 30 cc of a 50 per cent solution three times a day, may be an effective agent in maintaining the urine output in between the mercurial injections. (i) Theocalcin, 1 gm three times a day, may be useful. (j) The use of oxygen may quicken the speed of recovery.

* Casec may be used to increase the protein intake in order to keep the salt within the 2 gm limit

(k) Less frequently are pleural or abdominal taps required to free the patient of accumulation in these cavities since the introduction of the mercurial diuretics (l) With disappearance of the signs and symptoms of heart failure, mobilization is begun, the patient first sitting up in increasing amounts, then walking, then given lavatory privileges and then bath privileges, adding on each new increment slowly until he has attained as much activity as can be tolerated. (m) Usually the patient is kept on limited fluids, low salt, digitalis and perhaps mercupurin and ammonium chloride after discharge from hospital. It is better to *prevent* recurrence of failure than to try to get rid of it when it is present. After-care of the cardiac and keeping him free of failure are the most important features of therapy. All too frequently we see a patient recover from heart failure and then all medication is stopped because he has no longer signs of failure. A patient who has had heart failure precipitated by an acute episode such as pregnancy or labor or acute respiratory infection may not need to continue on digitalis or the other diuretics afterward. (n) In the management of a patient's activities, it is much better to have the patient remain in bed one half of the day and feel well while up, than to be up all day and feel fatigued at the end of the day or all the time while up. If any special event is coming up, prepare for it by extra rest, such as staying in bed all day if going out in the evening, rather than try to catch up after the overload has occurred.

5 *The care of acute respiratory infection is important.* Patients should be advised to remain in bed for a few days when there is an acute tonsillitis or acute respiratory infection, and to be on the alert for manifestations of recurrence of rheumatic infection ten days to two weeks later. The acute infection may precipitate heart failure in a patient with valvular disease who usually maintains compensation. If heart failure occurs it is treated as usual. Oxygen administration by tent or mask may lessen the load in the presence of an acute bronchitis. aminophylline 0.24 to 0.48 gm. may be given intravenously. The use of steam inhalations with *tincture* of benzoin every four hours for twenty minutes may lessen the wheezing and loosen the secretions. Penicillin or sulfadiazine may be used. Frequently acute bronchitis is confused with pneumonia.

6 We have patients who are kept ambulatory and working, leading active lives, who adhere to their regimen of reduced fluids, low salt, digitalis and mercupurin once or twice a week, for year after year after the first attack of failure.

7 Others are kept ambulatory with medication with their activities limited to their capabilities.

8 The Schemm regimen^{40 50} of high fluid intake and acid ash, low salt diet requires careful study in many controlled cases before a decision can be made whether it has a place in the treatment of cardiac edema.

9 *Digitalization of ambulatory patients* Satisfactory digitalization of ambulatory patients can be accomplished by a modification of the rapid method with the same precision as digitalization of patients in bed, if it is known by experience with the preparation of digitalis being used what the digitalizing amount is if given in twenty-four hours, together with the average maintenance amount. The digitalizing amount plus the total maintenance amount for the number of days which is decided upon for digitalization is spread over this period, the larger amounts are given early in the course and tapered off toward the end of the period (Stewart in Cecil²⁴)

10 *Mechanism of action of digitalis* Stewart and his associates have studied the effect of giving digitalis in patients suffering from rheumatic heart disease before onset of failure as well as during and after recovery from congestive heart failure^{27,28} During heart failure the cardiac output per minute and per beat is decreased, the circulation time prolonged, the venous pressure elevated and the heart large. With the administration of digitalis the heart size becomes smaller, the cardiac output increases per beat and per minute, the circulation time decreases and the venous pressure falls. The results are the same in patients with auricular fibrillation as in those with normal rhythm. The functional capacity on the average does not attain as high levels as before the occurrence of failure³⁸ From these and other studies it was thought that the determining effect of digitalis was on the size of the heart, namely a decrease in that the heart in failure was brought to a more effective size so that the normal heart as well as the heart in failure obey Starling's Law of the heart relating to the length of muscle fiber⁵¹

11 Christian⁵² advocated the use of digitalis in patients with heart disease *before* the onset of heart failure. Stewart and his associates^{27, 28} showed that even though digitalis decreased the size of the heart in patients with rheumatic valvular diseases before the onset of heart failure, and decreased the volume output of blood per minute, the work of the heart per beat was increased so that the work was more nearly appropriate for the size of the organ, these data afford some objective basis for Christian's clinical impression⁵² Following on with the inferences from our papers,^{27, 28} Erickson and Fahr⁵³ showed that patients with clinically compensated but organically diseased hearts showed improvement in mechanical efficiency when digitalized, while subjects with normal hearts showed impairment in cardiac function after digitalization. The greatest improvement in function occurred in those patients in whom the circulation time was sixteen to twenty seconds. They were of the opinion that digitalis was definitely indicated for organically diseased and enlarged hearts which appear compensated, when the circulation time is greater than sixteen seconds. A large group of patients will have to be observed over a long time before it can be decided whether the life histories

and span of such patients differ from those in whom digitalis is used only after the onset of heart failure.

12. At the time of tonsillectomy or tooth extractions sulfadiazine with sodium bicarbonate should be given the day before, the day of, and the day afterward in order, if possible, to forestall subacute bacterial endocarditis. Penicillin may be used for this purpose. With each respiratory infection the use of these two drugs should be considered but not used routinely.

PREGNANCY IN RHEUMATIC HEART DISEASE

In recent years the cardiac patient has been more satisfactorily treated during pregnancy. This has been the result (1) in some instances of the obstetrician taking a greater interest in this group of patients and acquiring an insight into valvular heart disease and the effects of pregnancy, and (2) in other instances the result of the attachment of internists or cardiac minded physicians to prenatal clinics and these men are guiding the care of cardiac patients.

1. If advice is sought about the advisability of pregnancy, careful examination to identify the valve lesions together with the evidence of cardiac insufficiency in history and on examination, form the basis of the decision. If the patient is young, has had no attacks of rheumatic infection for some time, and has had no signs or symptoms of cardiac insufficiency, there is good reason to believe that she should go through pregnancy without accident. A patient with aortic stenosis plus aortic insufficiency and mitral stenosis and insufficiency should be advised against pregnancy because studies made in this combination of defects show a marked decrease in their functional capacity.²³ If the patient is a multipara the pregnancy and labor are usually easier, and this is considered in arriving at the final decision. Each case has to be decided as an individual problem, but the use of the functional capacity criteria of the New York Heart Association Classification gives some uniformity. Careful supervision should be maintained during pregnancy, with rest in bed for colds and care given as described under the next two headings. Patients with auricular fibrillation should not become pregnant.

2. If the cardiac patient is seen early in pregnancy the decision has to be made between continuance of pregnancy and its termination. The same consideration is made as in heading 1 above with respect to continuing the pregnancy. If the patient has had frank heart failure occurring in the usual course of her activities. If the heart is very large, if auricular fibrillation is present and the patient is already taking digitalis and it is early enough in pregnancy therapeutic abortion is usually the wisest procedure. If the patient is allowed to go on she should be carefully observed and seen more frequently as pregnancy advances. It may be wise and necessary to put the patient to bed for the last months of pregnancy. Having arrived at this stage the question

then to be decided is whether to wait for spontaneous labor or to resort to cesarean section

3 If the patient is seen late in pregnancy, the patient is carried along as well as possible, in bed if necessary until term or until a viable baby can be obtained by cesarean section

Effect of Pregnancy and Labor on the Circulation.—The changes in the circulation during pregnancy have been studied by Stander⁵⁴ and by Burwell and his associates⁵⁵ The changes start around the fifth month and reach their peak at eight and one half months There is an increase in blood volume, increase in cardiac output, increase in oxygen consumption, and decrease in the arteriovenous oxygen difference These are basic changes to which are added the increased demands of labor which the heart may not be able to meet. Sampson, Rose and Quinn⁵⁶ have estimated the work of obstetric labor and its significance in heart disease They concluded that the work of labor in both primiparous and nulliparous women is the equivalent of mild to moderately heavy physical labor the degree of which cannot be predicted Cesarean section does not carry the danger of this unpredictable load of physical work, but presents risks of its own In making a decision about cesarean section it is kept in mind that cardiac patients tolerate surgery well and that ether with oxygen is the anesthetic which is best tolerated

The final effect of pregnancy on the cardiac patient has not been accurately determined by statistical means^{57, 58} No doubt the hazard has been greatly lessened by the cooperation of internist and obstetrician in the care of the cardiac patient Recent statistics of Boyer and Nadas⁵⁹ showed that the life expectancy was not shortened by pregnancies We have all seen certain patients, however, who have had their functional capacity greatly and permanently lowered by pregnancy The life span of female patients with rheumatic heart disease has a wide range and it is difficult to compare this with that of a parallel group who have had pregnancies in such a way that the statistics are valid

OTHER ASSOCIATED CONDITIONS

Rheumatoid Arthritis and Mitral Stenosis —Dawson states that in 100 consecutive cases of typical rheumatoid arthritis unequivocal signs of mitral stenosis were present in 7 per cent⁶⁰ He has observed obliteration of the pericardial cavity in the terminal stages of rheumatoid arthritis in adults Only the slightest changes are seen in electrocardiograms I had occasion to examine a series of electrocardiograms derived from patients with Still's disease and was unable to detect any changes that could be attributed to myocardial involvement⁶¹ I have not, myself, observed mitral stenosis in rheumatoid arthritis

Onset of Hyperthyroidism in Rheumatic Heart Disease.—When a patient with rheumatic heart disease has been adequately controlled and the heart rate increases or if the patient has auricular fibrillation and the ventricular rate increases and more digitalis is required to keep the ventricular rate slow the onset of Graves disease should be suspected, and the basal metabolic rate estimated. It is known that the basal metabolic rate increases in heart failure,⁶² which may lead to confusion. The circulation time may be helpful in this situation in the presence of heart failure and auricular fibrillation the circulation time should be prolonged but if it is short, or in the normal range, this is evidence of increased thyroid activity speeding up the circulation.

TERMINAL EVENTS IN RHEUMATIC HEART DISEASE

A patient may escape or survive the accidents, already described to which these patients are prone. They may have had repeated attacks of heart failure in the course of years requiring complete bed rest, with varying degrees of activity in between. With each recurrence of failure the ease of restoration of compensation is less and, as time goes on, the diuretics become less effective. This span has been increasing with the use of the mercurial diuretics and better care of cardiacs. The heart has been getting larger. Ventricular premature contractions appear. The heart muscle increases in irritability, the administration of adequate digitalis commensurate with that expected to control heart failure induces frequent ventricular premature contractions up to coupling and then they become multiple and short runs of ventricular paroxysmal tachycardia appear. At this stage the physician has to be content with giving the maximum amount of digitalis that can be taken as a maintenance dose with the least toxicity.

PREVENTION OF RECURRENCE OF RHEUMATIC INFECTION

The prevention of rheumatic fever is laden with more than the usual difficulties because the etiological agent is not known. The occurrence of streptococcus sore throat followed in ten days to two weeks by acute rheumatic fever occurs too frequently to be a chance phenomenon. Nothing however, can be done at the present time in the general population to prevent the occurrence of rheumatic fever except those measures directed at general hygiene, avoidance of overcrowding, adequate diet and the like. Epidemics of rheumatic fever have been described.⁶³ What can be done to prevent recurrences in an individual who has had rheumatic fever?

1. *The use of a daily ration of one of the sulfa drugs* has been tried^{64 65 66 67 68 69 70} and found to reduce the number of expected recurrences. Holbrook⁷¹ in the Army Air Force by the use of sulfa diazine was able to reduce the incidence of respiratory disease and

streptococcal infections and establish a parallel decrease in the incidence of rheumatic fever. Such a procedure is not applicable at the present time to the general population. I do not think that adequate experience has been gained to justify the use of sulfadiazine in general practice for the prevention of recurrence of rheumatic infection. If anyone wishes to observe a series it may be done provided careful supervision is given to blood levels of the drug and blood counts, in order to detect any incipient toxic effects.^{72, 73, 74, 75}

2 Coburn found that the use of daily rations of salicylates prevented recurrence of rheumatic fever.⁷⁶ This finding, however, has not been convincing enough to put to general use.

3 *Change of environment*. Coburn⁷⁷ moved a group of patients subject to recurrent rheumatic fever from New York to the tropics. It was found that while in residence in Puerto Rico they did not have recurrence of rheumatic fever, but that recurrence occurred when they returned to New York. This is a procedure which is applicable to a small group of patients and may be used to get them past the adolescent period when recurrence is more persistent. It is seldom satisfactory to send patients to Florida for this purpose because the constant flow of the population back and forth often brings the respiratory infections to the southern location.

SOCIAL AND ECONOMIC LOSS FROM RHEUMATIC HEART DISEASE

Rheumatic fever and its consequences are among the most devastating of all diseases in so far as the social and economic loss of the individual and society is concerned. The maximum incidence of rheumatic fever is at 10 years of age. From the beginning of infection to established heart disease is one to eight years, the average being four years, from the establishment of heart disease to onset of heart failure is seven years, and from heart failure to death four years. This gives fifteen years as the average duration of rheumatic heart disease (Cohn^{29, 30}). DeGraff³⁷ arrives at approximately the same data in another way: the average age of infection is 17 years, the average age of the first symptoms of heart disease is 28 years (i.e., eleven years after infection), the average age of first appearance of failure is 30 years (i.e., two years after first symptoms), the average age of death is 33 years (three years after first failure), making the span of the rheumatic heart disease sixteen years. What does this mean to the individual? Rheumatic fever begins around 10 years of age during the school period. The patient is handicapped by recurrence school year after school year, the progress of the disease is apparent during his adolescence and during his preparation for assuming economic care of himself by learning a profession or trade, heart failure comes on when he is in the prime of his career and death occurs while he is at what would ordinarily be the most productive period, in short before social and economic benefits have been reaped.

So much for the drab side of rheumatic heart disease relating to the average patient. The life history of a patient who had rheumatic heart disease will be briefly recounted to show what can be accomplished with cooperation of the patient with the physician

CHRONOLOGICAL HISTORY OF A RHEUMATIC FEVER PATIENT

The following is the chronological story of the rheumatic history of a woman who was a singer New York Hospital History Number 46789

AGE	
7 years	Acute rheumatic fever (typical)
9 years	Second attack of acute rheumatic fever
11 years	Third attack of acute rheumatic fever
12-13 years	Chorea for one year
13 years	Fourth attack of acute rheumatic fever Heart disease discovered.
22 years	First and only attack of acute tonsillitis
24 years	Slight edema at night.
26 years	Dyspnea orthopnea edema at end of pregnancy
29 years	Fifth attack of acute rheumatic fever
36 years	Tonsils removed, thought it good for her singing
42 years	Slight fatigue She observed irregularity of heart.
43 years 6 mos	Dyspnea on playing golf Limited her activities herself Oppression in epigastrium and over precordium.
43 years 10 mos	Increasing dyspnea, and fullness in abdomen. Began taking digitalis and staying in bed one day each week.
44 years	Admitted to St. Luke's Hospital, New York, for treatment to slow the ventricular rate.
44 years 3 mos.	First attack of heart failure. First admission to Hospital of Rockefeller Institute for 2½ months because of shortness of breath, dyspnea on talking auricular fibrillation was present, few rales on deep inspiration, ascites No edema. Improved and discharged on digitalis which was continued except when specifically mentioned as being discontinued.
45 years	Giving singing lessons and doing church singing on Sundays Ventricular rate rapid.
46 years 2 mos.	Gave up choir singing. Feels bad if she gets up early Enlarged liver
47 years	Does not feel well. Doing choir work and some teaching Ventricular rate rapid. Liver below umbilicus Ascites. No edema
47 years 2 mos.	Second attack of heart failure. Admitted to Hospital of Rockefeller Institute for 17 days. Had been doing choir work and teaching until admission. Cyanosis Slight respiratory distress Heart enlarged. Mitral stenosis and insufficiency Ascites. No edema. To rest 1 or 2 days each week

- 47 years 5 mos Third attack of heart failure Admitted to Hospital of Rockefeller Institute for 3 months Edema and shortness of breath. *Gave up digitalis* on own accord several weeks ago because she was discouraged but continued to limit fluids Marked dyspnea, cyanosis, orthopnea Pulmonary congestion, ascites and edema Patient again digitalized and discharged on maintenance doses four times a day
- 48 years No signs of congestive heart failure Stays in bed part of each day
- 49 years 6 mos No signs of congestive heart failure Wishes to start singing again To arrange life to stay in bed in morning
- 50 years 6 mos No signs of congestive heart failure except liver enlargement. Has remained well
- 50 years 8 mos Occasional swelling of legs—transient
- 51 years Ascites increasing Ankles swelling Is not spending much time in bed Goes to bed at 3 or 4 A.M.—gets up at 1 or 2 P.M. Goes downtown and wherever she wishes, taking a cab Slight dyspnea and cyanosis, Some ascites Liver nearly to crest of ilium Bed rest. *Digitalis Theocalan*
- 51 years 6 mos Edema and ascites returned following train trip Remained in bed
- 51 years 8 mos Fourth attack of heart failure First New York Hospital admission—46 days Generalized skin eruption (*dermatitis medicamentosa*) from salyrgan Discharged on low salt, restricted fluids, *digitalis* Ascites was present, and slight pitting edema.
- 51 years 10 mos Feeling well. In bed till noon and has been out on several occasions without dyspnea Lungs clear Auricular fibrillation with slow rate continues
- 52 years 4 mos Condition good Remains in bed now and then for a day or two Lungs clear Liver enlarged Abdomen a little fuller No edema
- 52 years 6 mos Fifth attack of heart failure precipitated by a respiratory infection Second New York Hospital admission—17 days Cough, dyspnea, ascites, orthopnea, nausea and vomiting, after catching a cold 6 days before Improved on oxygen therapy and *digitalis*
- 54 years Sixth attack of heart failure Third New York Hospital admission—24 days Since discharge spends most of time in bed. Slow increase in ascites for past 5 months Receiving intravenous aminophylline with fair results Ascites returning, increasing dyspnea, no edema Liver 12 cm below the right costal margin Received mercupurin and urea solution 50 per cent with clearing of failure
- 54 years 1 mo Seventh attack of heart failure precipitated by acute bronchitis Fourth New York Hospital admission—14 days Stayed at home, going out on only two occasions Continued *digitalis* and cardiac regimen, taking urea solution daily Progressive increase in size of abdomen and swelling of legs Pulmonary congestion and bronchitis on admission Ascites and edema

Put on bed rest, oxygen for 24 hours Five injections of mercuripurin with improvement

- 54 years 4 mos. Eighth attack of heart failure Fifth New York Hospital admission—12 days Since discharge has had frequent head colds with sore throat. Cold for 3 weeks, attended by increasing dyspnea and orthopnea. Increasing ascites Fever 101.6° F Distended neck veins rales in left lung Enlarged liver No edema On digitalis mercuripurin with good response
- 55 years 1 mo Ninth attack of heart failure Sixth New York Hospital admission—10 days Getting along well until 6 days before admission when she became fatigued. Head cold with cough ankles swelling, dyspnea, orthopnea Cyanosis Improved in 2 days with oxygen Good diuresis with mercuripurin and ammonium chloride. Continued slow fibrillation.
- 55 years 4 mos Abdomen getting larger Liver enlarged. Requires mercuripurin injections every 3 days to prevent recurrence of ascites. Up and about most of the time Short walks out of doors On low salt and fluid regimen.
- 55 years 6 mos Tenth attack of heart failure precipitated by acute bronchitis Seventh New York Hospital admission—8 days Cough dyspnea, orthopnea, and ankle swelling developed after acute upper respiratory infection. Rales at lung bases. Minimal edema On cardiac regimen, oxygen digitalis and mercuripurin improved. Diagnosis Acute bronchitis
- 55 years 8 mos Capable of moderate degree of activity without stair climbing Can walk fair distance without difficulty Well during spring and summer on mercuripurin at 5 or 6 day intervals Salt free diet, and fluids limited to 1200 cc. Questionable early signs of tricuspid insufficiency first noted. Liver reaches crest of ilium
- 56 years Eleventh attack of heart failure. Eighth New York Hospital admission—8 days Admitted because of poor response to mercuripurin and progressive ascites Dyspnea orthopnea, cyanosis Venous pressure 170 mm saline Lungs clear Auricular fibrillation, ventricular rate 76 Ascites Tender liver with questionable pulsation. Slight ankle edema. In oxygen tent for four nights Good response to mercurials Tricuspid insufficiency
- 56 years 4 mos. Remaining in bed except for biweekly visits to her doctor
- 56 years 5 mos. Twelfth attack of heart failure Ninth New York Hospital admission—13 days Ascites distention and constipation with progressive orthopnea and exertional dyspnea of 2 weeks duration Rales at lung bases Totally irregular rhythm. Distended veins over anterior chest. Bed rest, limited fluids and salt, 0.1 gm. digitalis daily Oxygen Mercuripurin 3 cc. every 3rd day Gradual improvement and discharged on 13th day
- 56 years 6 mos Thirteenth attack of heart failure. Tenth New York Hospital admission—57 days Since discharge fatigue dyspnea and orthopnea in spite of avoiding all activity except coming to the hospital twice weekly for mercuripurin injections Increasing ascites and edema Cyanosis engorged veins Auricular fibrillation (78/min) Scattered rales at both bases Marked

cites Enlarged liver Three plus pitting edema of ankles On bed rest, oxygen, 1200 cc fluids and 2 gram salt diet Mercupurn 3 cc every 3 days One paracentesis (9th day)—2650 cc removed Gradual improvement, signs of failure became less

56 years 6 mos On digitalis 0.1 gm two or three times daily Mercupurn bi weekly Protein diet 100 gm. On bed rest with bathroom privileges Complete bed rest after 1st week when dyspnea and ascites recurred Nausea developed. High protein diet reduced Paracentesis at home

56 years 10 mos Fourteenth attack of heart failure Eleventh New York Hospital admission—5 months 5 days Rapid reaccumulation of fluid, dyspnea Physical findings Apical rate 86, pulse rate 80, blood pressure 125–115/55 mm Dyspnea, orthopnea, cyanosis. Engorgement of neck and chest veins Venous pressure 200 mm saline Rales at base of left lung Heart enlarged all diameters Auricular fibrillation present. Ascites Tender liver 6 to 7 fingerbreadths below the costal margin Pitting edema of sacrum, thighs and legs Course Put on 3 gm salt diet and fluids to 1200 cc Oxygen Mercupurn (later discontinued because of pruritus) Aminophylline (discontinued because of reaction) Course progressively downhill with increasing anasarca Nausea and vomiting developed and persisted Response to mercupurn less and less Pulmonary edema developed

57 years 3 mos Expired after 5 months 5 days hospitalization

CLINICAL DIAGNOSIS

Rheumatic Heart Disease, Inactive

Mitral Stenosis

Mitral Insufficiency

Functional Tricuspid Insufficiency

Chronic Auricular Fibrillation

Cardiac Enlargement

Chronic Passive Congestion of Liver and Kidneys

Pulmonary Edema

Ascites

Edema of Cardiovascular Origin

Permission for autopsy was given

ANATOMICAL DIAGNOSIS (Autopsy Findings)

Primary

Chronic endocarditis of mitral valve with stenosis and insufficiency

Fibrous thickening of leaflets of aortic valve

Hypertrophy and dilatation of left auricle, hypertrophy of right ventricle

Thrombus in left auricular appendage

Fibrous obliteration of pericardium

Dilatation of pulmonary artery with arteriosclerosis (moderate)

Chronic passive congestion of lungs, liver, spleen and intestines

Cirrhosis of the liver

Hydrothorax, right, 300 cc

Ascites, 2600 cc

Dilatation and sclerosis of inferior vena cava and renal vein

Edema of extremities

Healed infarcts of kidney

Focal vascular scars of kidneys

Accessory

Calcified tuberculous nodules of lungs and tracheobronchial lymph nodes.

Fibrous pleural adhesions over both lungs.

Carcinoma of the pancreas

Fibromyomata uteri.

Hemorrhagic cyst of right ovary

Arteriosclerosis of coronary arteries and aorta (moderate)

Chronic cholecystitis and cholelithiasis.

Accessory spleen.

Melanosis coli

Organized bronchopneumonia (microscopic)

Healed duodenal ulcer

As this life history is viewed as a whole we see a woman who started having rheumatic fever at 7 years of age, was known to have rheumatic heart disease since 13 years of age, who had one pregnancy who earned her living until the last few years of her life, and who lived to be over 57 years of age. She is known to have had auricular fibrillation for the last thirteen years of her life. She managed well until the onset of her first failure at 44 years. For the next three years there was moderate restriction of her activities. After that she began to remain in bed part of the day or certain days of the week, so that she felt well the part of the day she was up. If doing anything special in the evening she remained in bed all day so that she felt well and comfortable, for instance, when she went to the opera. Then the frequency of attacks of failure requiring complete bed rest increased, and there was an accelerated pace over the ensuing years as the functional capacity of the heart decreased. Many of the later episodes were precipitated by acute respiratory infections or acute bronchitis. If the sulfa drugs and penicillin had been introduced at that time they might have been used for these episodes. She had recovered from failure so many times that hope was constantly entertained by the patient that she would recover from the final attack. In spite of her handicap she remained active for the part of the day she was up was mentally alert in reading, literature and music. She cooperated wholeheartedly in carrying out her program of treatment and management when she was on her own out of the hospital. She learned to count her heart rate without any morbid interest and managed her digitalis dosage in a manner which could not be improved upon. She enjoyed a rich life and displayed courage which has been an inspiration and help to me in taking care of other patients with heart disease.

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SUSCEPTIBILITY OF THE HOST IN RHEUMATIC FEVER*

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It is an accepted fact that certain individuals are more susceptible than others to the acquisition of many diseases. In recent years it has become clear that the character of the host is one important factor in resistance and susceptibility. The biological pattern of development of an individual is determined both by his hereditary constitution and his environment during his life experience.

That hereditary factors are implicated in the familial concentration of rheumatic fever has long been suspected. Recent genetic and epidemiological studies^{1, 2} have demonstrated that susceptibility to rheumatic fever depends primarily upon the genetic constitution of the individual and his chronological age. It was found that the distribution of cases in rheumatic families follows the general laws of recessive mendelian inheritance.

It is to be emphasized that a disease may not be considered hereditary on the basis of a high familial incidence alone; nonhereditary factors must be excluded and the hypothesis must be substantiated by adequate genetic analysis. Statements about heredity in any condition refer to explicit cellular and functional attributes and properties whose precursors have a concrete and real existence in the genes. Although heredity may underlie abnormal physiological, chemical or hormonal responses in the genetically susceptible host, a variety of exogenous factors may be necessary for the expression of the condition in the susceptible host, without which the condition will fail to be expressed altogether.

GENETIC RISK

The susceptible child cannot be identified at the present time. However, biostatistical methods of analysis are available which permit the prediction of the genetic-age risk for any child in a family to develop an initial or subsequent attack of rheumatic fever.²

In the accompanying tabulation the genetic distribution for a recessive trait is illustrated for six hypothetical families of different genotypes having four children each. In family A, where both parents are rheumatic, the four siblings are genetically susceptible. There are few families of this genotype in the general population, but whenever they are observed it may be assumed that all children will be genetically

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DISTRIBUTION OF SUSCEPTIBLES, CARRIERS AND NORMALS IN VARIOUS TYPES OF MATINGS ON THE POSTULATE
OF RECESSIVE INHERITANCE

Mating	Parent Genes	Possible Gene Combinations for Siblings	Distribution in Families Having at Least Four Siblings		
			Susceptibles (Cases)	Carriers	Normals
A. Both parents rheumatic	xx	xx	1	0	0
B. 1 parent rheumatic, 1 parent carrier	xy	xx	2	2	0
C. 1 parent rheumatic, 1 parent normal	xx	xy	0	4	0
D. Both parents carriers	xy	xx	1	2	1
E. 1 parent carrier 1 parent normal	xy	xy	0	2	2
F. Both parents normal	yy	yy	0	0	4

x = Rheumatic
y = Nonrheumatic

susceptible In family B, where one parent is rheumatic, and the other parent is nonrheumatic but a carrier, if there are four children, two will be genetically susceptible and two will be carriers That is, each child has a 50 per cent chance to be either genetically susceptible or a carrier In family C, where one parent is rheumatic and the other parent is nonrheumatic, there will be no genetically susceptible offspring, but every child will be a carrier This type of family is not represented in a group of families selected on the basis of clinic attendance In family D, where both parents are carriers, there will be one genetically susceptible child, two carriers, and one negative child That is, each child has a 25 per cent chance to be a genetic susceptible, a 50 per cent chance to be a carrier, and a 25 per cent chance to be negative This is probably the most common genotype observed, when a rheumatic child having nonrheumatic parents is brought to a clinic It is apparent that the absence of a rheumatic history in the parents does not exclude a positive family history completely, because of the high carrier rate In family E, where one parent is a carrier and the other parent is negative, there will be no genetically susceptible children, but two children will be carriers and two will be negative Families of this genotype are not represented in groups selected on the basis of clinic attendance In family F, where both parents are negative, all children are negative, and there is no possibility for genetic susceptibility to rheumatic fever or a carrier rate in the offspring

The genetic analysis of a series of rheumatic families in a clinic population in New York City revealed that the number of genetic susceptibles estimated was found to be in close agreement with the final number of cases observed It therefore may be postulated that distributed in the population are individuals who are susceptible or insusceptible to the development of rheumatic fever This genetic predisposition is a constant factor which is present from birth to death Whether the disease will actually develop in such an individual may be dependent upon other factors At the present time it cannot be concluded that every genetically susceptible child will necessarily develop rheumatic fever It is probable that genetic analyses of a comparable series of rheumatic families would also show close agreement between the number of genetic susceptibles predicted and the number of cases observed Whether genetic studies of families in various geographical localities or different economic groups would also be comparable must await the result of such investigations It must be emphasized, however, that although the frequency of cases may vary the distribution of genetic susceptibles should not

AGE RISK FOR ONSET

The Age Expression of Rheumatic Fever.—The age expression of rheumatic fever is probably one of the most important factors in the

evolution of the disease. It has long been observed that rheumatic fever usually develops during childhood, from the age of 4 years to puberty, with an average age of onset at about 6 years. As Paul has aptly stated, "The infant must grow up to be rheumatic." There is an age factor in rheumatic fever which must be taken into account as well as the genetic background. For example, an infant, both of whose parents are rheumatic and who therefore has almost a 100 per cent chance to be rheumatic on a genetic basis, would not be expected to show symptoms of the disease until he had reached the age of at least 4 years.

The age risk in rheumatic fever may be expressed by the incidence of case onsets at various ages. Such incidence rates represent the average chance a genetically susceptible child has for developing rheumatic fever at any particular age. Since the peak age at onset occurs at about 6 years in children, it is apparent that the age risk for a 2 year old child or a 12 year old child is less than that for his 6 year old sibling.⁴

In a series of families, values for the genetic risk and the age risk were applied in combination, making it possible to predict the annual incidence of onsets of primary and secondary cases during the life experience of these families. That is, the intrafamilial pattern of spread of rheumatic fever was completely described by the use of age and genetic factors.

These observations are of epidemiological significance. They demonstrate that whatever factors are responsible for the onset of rheumatic fever among susceptibles they were uniformly operative and effective during the entire life experience of these families. Furthermore, they demonstrate that rheumatic fever does not exhibit the usual characteristics of a communicable disease. It is unlikely that comparable observations could be obtained in any known infectious disease. On the other hand, similar findings might be demonstrated in a series of diabetic families.

It is not within the scope of this presentation to attempt to define the nature of the inherent defect or to interpret the age expression of the disease. At the present time it may be concluded that heredity is primarily responsible for the familial incidence of rheumatic fever and that the age risk determines the time of occurrence of cases in the family.

Risk of Recurrent Attacks.—The clinical course of rheumatic fever is characterized by frequent recurrence of manifestations of the disease and a varying number of intercurrent years of apparent freedom from symptoms. Since current etiological concepts and consequent preventive therapy are based in large measure on a comparison of the number of recurrences among experimental and control groups of rheumatic patients, it is important to define the average risk of a recurrence of rheumatic fever.

Age Risk.—The expected risk of an overt recurrence of rheumatic fever (arthritis, chorea, active carditis) was determined in a large series of patients representing 5600 person years of life experience. It was found that the average over-all risk of a major recurrence was 25 per cent for patients between the ages of 4 and 13 years, 9 per cent for those between 14 and 16 years and about 4 per cent for those 17 to 25 years of age. It is obvious that the risk of recurrence varies significantly with the age of the patient.

Of particular importance was the observation that the risk of recurrence during the year immediately following a major episode was twice as great as that following at least one year of freedom, and three times as great as that following at least two years of freedom from symptoms.

Contrary to expectation, there were neither "good years" nor "bad years" for rheumatic fever, that is, the rate of recurrence was not found to vary in twelve consecutive calendar years. It was also observed that the risk of recurrence did not appear to be affected by the number or severity of previous attacks.

Preventive Therapy.—The expected risk of a major manifest recurrence of rheumatic fever is useful in evaluating the results of prophylactic therapy. Awareness of the importance of rheumatic fever has stimulated renewed efforts for its prevention. Current etiological concepts form the basis for prophylactic therapy. In the present state of our knowledge of rheumatic fever, this approach is valid. If prophylactic therapy proves successful, in addition to the prevention of the disease, evidence for a basic etiological concept would be obtained.

The recently reported favorable results of sulfonamide prophylaxis have been widely accepted. Thomas, summing current published studies, observed that of 815 patient seasons over a period of seven years the incidence of recurrence in the treated groups was 1 per cent compared with 10 to 35 per cent in the untreated control groups. If these results are valid, the conclusion that *all* rheumatic children should receive prophylactic therapy "day in and day out" would be justified^{6, 7}.

However, critical analysis of published studies revealed that the individual studies did not meet the basic requirements for adequate biostatistical analysis. Selective and inadvertent bias characterized most studies. Rarely were alternate experimental and control patients selected. Frequently patients were shifted back and forth between experimental and control groups. Such patients were usually those who were uncooperative and refused treatment.

In many studies, the experimental and control groups were not comparable because of differences in age constitution or variations in the length of time elapsing since the previous attack. In the majority of studies the groups were too small, and final conclusions were usually

based on summated observations. This practice is only acceptable provided that each study which is included represents a random selection of patients. In addition, diagnostic criteria and observation must be uniform, environmental conditions and age constitution comparable. The published studies which have been summated in rheumatic fever do not appear to meet these requirements. It is obvious that final judgment as to the validity of the etiological concept and consequent preventive therapy which are based on these studies must be deferred.

CONCLUSION

The biostatistical methods of analysis which have been applied to rheumatic fever have provided fundamental data on the nature of the risk for developing the disease, for onsets as well as recurrences. They indicate that the most important factor in the pathogenesis of rheumatic fever is susceptibility of the host. Future studies may reveal the nature of the factors responsible for the development of rheumatic fever among genetic susceptibles of a susceptible age.

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THE INCIDENCE OF ABNORMAL ORONASAL LYMPHOID TISSUE IN RHEUMATIC FEVER PATIENTS

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THE initial attack of rheumatic fever and, to a lesser extent, most recurrences of rheumatic disease are preceded by an acute infection of the upper respiratory tract. The infection preceding the initial attack is either a severe pharyngitis, tonsillitis, nasopharyngitis, or a severe cold. The oronasal lymphoid tissue provides the initial point of entry for infection.

In order to determine the incidence of abnormal oronasal lymphoid tissue in rheumatic fever patients, a study was conducted in two large AAF hospitals in the southern states. Two hundred and fourteen soldiers who had clinically active rheumatic fever or were convalescent or designated as recovered from the disease were examined. The men varied in age from 19 to 35 and had been transferred from stations located in regions where the incidence of upper respiratory infection and rheumatic fever was high. The time between the onset of the upper respiratory infection and the initial or most recent recurrent attack of rheumatic fever varied from two weeks to nine months.

HISTORY

Ninety per cent of the subjects gave a history of tonsillitis, or severe nasopharyngitis, scarlet fever, sore throat or cold prior to the onset of joint manifestations. Those in whom sore throat preceded the original attack of rheumatic fever described the sore throat as the most severe ever experienced, the discomfort lasting from seven to twenty-one days. In those patients having recurrence of rheumatic disease, the precipitating factors were variously described as sore throat, slight cold, overexertion, exposure or injury. Past incidence of upper respiratory infections was determined and recorded as normal or excessive. Excessive colds were reported in 33 per cent, 65 per cent gave a history of tonsillitis or streptococcal sore throat of sufficient severity to cause temporary disability. Over 50 per cent of all the subjects examined gave a history of increased susceptibility to colds following entry into military service and a higher percentage volunteered the information that resistance to respiratory infections had been noticeably impaired since the onset of rheumatic fever. Additional items noted in the history were the incidence of otitis media, sinusitis, allergy, cervical adenitis and ear, nose and throat operations.

EXAMINATION

The nose was examined for evidence of sinusitis, allergy, obstruction or other disease. Sinusitis was present in fourteen of the men, nasal allergy in six. The incidence of both conditions was surprisingly low.

The oropharynx was examined for abnormal tonsils or tonsil remnants and the posterior pharyngeal wall for abnormal lymphoid tissue deposits. Evidence of enlarged cervical nodes was sought.

The ears were examined for middle ear disease and indication of eustachian tube obstruction. Inactive, nonsuppurative otitis media was present in two patients.

Since the nasopharynx is of primary interest in this study, it might be well to describe the criteria by which nasopharyngeal lymphoid tissue is designated as normal or abnormal. The normal adenoid and pharyngeal tonsil is centrally placed and presents three to five vertical fissures and lobulations. In persons of the age group of 19 to 35, with which we are concerned, it does not exceed 0.5 cm in depth. It may be completely atrophied. The color is grayish pink and similar to the color of the normal posterior pharyngeal wall. The surface is smooth and glistening and there is no evidence of infection. It does not encroach upon the fossa of Rosenmüller or the pharyngeal end of the eustachian tube. The torus of the eustachian tube and the tube itself are free of lymphoid tissue deposits. The fossa of Rosenmüller is not obstructed by lymphoid tissue or adhesions. Any amount of lymphoid tissue or disease that is not consistent with the foregoing is considered to be abnormal.

In this study the nasopharynx was examined by postnasal mirror and nasopharyngoscope. Bacterial cultures were taken from the throat and, when the tonsils were present, from the tonsil crypts. Cultures were taken from the nasopharynx by direct vision through the nose. As a control, 200 normal individuals (soldiers) in the 19 to 35 age group were examined. Thirty-two per cent, or approximately one-third, were found to have abnormal oronasal lymphoid tissue.

The 214 subjects of the original study have been divided into two clinical groups. 1. The first group was comprised of patients presenting various degrees of clinically active rheumatic fever who were still undergoing hospital treatment. There were ninety-one patients in this group. 2. The second group included those patients showing no clinical evidence of active rheumatic fever who had been designated as convalescent, had either returned to duty or were in various stages of convalescent training. There were 123 patients in this group.

In group 1, sixty-eight patients or 74.8 per cent, exhibited abnormal nasopharyngeal lymphoid tissue. Forty-eight patients or 52.6 per cent had abnormal and infected tonsils and twelve patients had tonsil remnants of sufficient size and appearance to indicate removal. In twenty-three patients or 25.2 per cent the nasopharyngeal lymphoid tissue was considered normal. Twenty-four patients, or 26.3 per cent,

gave a history of excessive colds and sixty-seven, or 73.6 per cent, gave a history of severe tonsillitis. Beta hemolytic streptococci were obtained by throat culture in 53.8 per cent and from the nasopharynx in 17.5 per cent of this group.

In group 2, sixty subjects, or 48.8 per cent, had abnormal nasopharyngeal lymphoid tissue. Sixty-two, or 50.4 per cent, had diseased tonsils and seven had tonsil remnants of such nature that removal was indicated. Sixty-three of the men, or 51.2 per cent, were considered to have normal nasopharyngeal lymphoid tissue. Forty-seven of the subjects, or 39 per cent, gave a history of excessive colds and seventy-two, or 59 per cent, gave a history of severe tonsillitis. On culture, beta hemolytic streptococci were recovered from the throat in 30.9 per cent and from the nasopharynx in 14.6 per cent.

DISCUSSION

Abnormal lymphoid tissue in the upper respiratory tract is easily infected. It provides the point of entry for the majority of upper respiratory infections. This is especially true in the nasopharynx. The recurrence of rheumatic fever is more or less directly related to the incidence of upper respiratory infection. Schlesinger¹ states "It is no exaggeration to say that acute nasopharyngeal infection is the most serious menace to the rheumatic child with heart disease. Relapses unprecedented by throat infections have been rare. The problem is centered in the pharynx. It seems that if outbreaks of throat infection could be avoided relapses would practically never occur." The same writer emphasizes the mild character of the throat infection and the quiescent period of seven to twenty-one days that ensues before the relapse of rheumatic fever. He further states that such infections are frequently overlooked as the cause of the relapse.

The rheumatic fever patients examined in this study exhibited an unusually high incidence of abnormal nasopharyngeal lymphoid tissue. This condition was present in 48.8 per cent of the convalescent group. The danger of relapse in these individuals is obviously greater than in those with a normal nasopharynx. The nasopharynx is frequently neglected as a site of infection. Inspection of the oropharynx often gives no clue to the presence of nasopharyngeal disease. Severe acute infection may be lurking above the palate only to be revealed by the postnasal mirror and nasopharyngoscope. The presence of this tissue also appears to bear some relationship to the prolonged activity of rheumatic fever. Of these patients showing active rheumatism, 74.8 per cent had abnormal nasopharyngeal findings. Attention to this area early in the disease might greatly shorten the period of hospitalization and disability. Robey and Finland,² reporting 165 patients upon whom tonsillectomy was performed, state "The earlier the focus of infection

is discovered, the greater the possibility of lessening the recurrence of attacks, the length of time in the hospital and danger of cardiac involvement."

TREATMENT

This survey does not include the actual treatment of any of these patients, however, the indications and type of treatment recommended were recorded in each instance at the time of examination. Such recommendations were based on otorhinolaryngologic evaluation and with full recognition of the presence of rheumatic disease.

The question of tonsillectomy is one of great controversy and has been the subject of extensive debate. Medical literature affords ample testimony to support anyone's personal views. The greatest amount of literature deals with the problem in early childhood. Certainly in adults in whom the history and examination show the presence of diseased tonsils the operation is indicated and should be done as soon as the possibility of precipitating a relapse is past. The removal of tonsils alone is not enough. The problem is only partially solved if diseased lymphoid tissue is allowed to remain in the nasopharynx. Perhaps it is because of this that tonsillectomy in rheumatic fever has been the subject of so much controversy and has proved to be a disappointment in so many instances.

Infections of the oronasal lymphoid tissue, when bacterial cultures reveal susceptible organisms, may be eliminated or neutralized by chemotherapy and the use of penicillin before operation and during the postoperative period, thereby obviating the dissemination of such infection by operative trauma. In a small series of patients convalescent from acute exudative nasopharyngitis caused by beta hemolytic streptococci, in whom repeated nasopharyngeal cultures were positive, by the use of penicillin nose spray (1000 units per cc., three times daily) it was possible to eliminate surface organisms for four to five days. Cultures became positive again when the spray was discontinued. This, of course, demonstrates the need for a parenteral concentration of penicillin to eliminate organisms within infected tissues. The topical use of antibiotics alone is not considered adequate to combat infection.

The treatment of abnormal lymphoid tissue in the nasopharynx, if large in amount, is surgical removal supplemented by the use of radium by Crowe's method.³ Smaller amounts may be treated by radium alone. The nasopharyngeal radium applicator offers a safe method for removing this tissue with a minimum of local disturbance. Since the only contraindication to the use of radium would be the presence of acute infection in the pharynx, irradiation of the nasopharynx may be started early in the course of the rheumatic attack. The beneficial effect of irradiation on subacute and chronic infections is well recognized.

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The oropharynx was examined for abnormal tonsils or tonsil remnants and the posterior pharyngeal wall for abnormal lymphoid tissue deposits. Evidence of enlarged cervical nodes was sought.

The ears were examined for middle ear disease and indication of eustachian tube obstruction. Inactive, nonsuppurative otitis media was present in two patients.

Since the nasopharynx is of primary interest in this study it might be well to describe the criteria by which nasopharyngeal lymphoid tissue is designated as normal or abnormal. The normal adenoid and pharyngeal tonsil is centrally placed and presents three to five vertical fissures and lobulations. In persons of the age group of 19 to 35, with which we are concerned, it does not exceed 0.5 cm. in depth. It may be completely atrophied. The color is grayish pink and similar to the color of the normal posterior pharyngeal wall. The surface is smooth and glistening and there is no evidence of infection. It does not encroach upon the fossa of Rosenmüller or the pharyngeal end of the eustachian tube. The torus of the eustachian tube and the tube itself are free of lymphoid tissue deposits. The fossa of Rosenmüller is not obstructed by lymphoid tissue or adhesions. Any amount of lymphoid tissue or disease that is not consistent with the foregoing is considered to be abnormal.

In this study the nasopharynx was examined by postnasal mirror and nasopharyngoscope. Bacterial cultures were taken from the throat and, when the tonsils were present, from the tonsil crypts. Cultures were taken from the nasopharynx by direct vision through the nose. As a control, 200 normal individuals (soldiers) in the 19 to 35 age group were examined. Thirty-two per cent, or approximately one-third, were found to have abnormal oronasal lymphoid tissue.

The 214 subjects of the original study have been divided into two clinical groups. 1. The first group was comprised of patients presenting various degrees of clinically active rheumatic fever who were still undergoing hospital treatment. There were ninety-one patients in this group. 2. The second group included those patients showing no clinical evidence of active rheumatic fever, who had been designated as convalescent, had either returned to duty or were in various stages of convalescent training. There were 123 patients in this group.

In group 1, sixty-eight patients or 74.8 per cent had abnormal nasopharyngeal lymphoid tissue. Forty-eight patients or 52.7 per cent had abnormal and infected tonsils, and twelve patients or 13.2 per cent had remnants of sufficient size and appearance to be considered abnormal. In group 2, twenty-three patients, or 25.2 per cent, had abnormal nasopharyngeal lymphoid tissue. Twenty-four patients or 26.8 per cent had abnormal and infected tonsils, and twelve patients or 13.2 per cent had remnants of sufficient size and appearance to be considered abnormal.

gave a history of excessive colds and sixty-seven, or 73.6 per cent, gave a history of severe tonsillitis. Beta hemolytic streptococci were obtained by throat culture in 53.8 per cent and from the nasopharynx in 17.5 per cent of this group.

In group 2, sixty subjects, or 48.8 per cent, had abnormal nasopharyngeal lymphoid tissue. Sixty-two, or 50.4 per cent, had diseased tonsils and seven had tonsil remnants of such nature that removal was indicated. Sixty-three of the men, or 51.2 per cent, were considered to have normal nasopharyngeal lymphoid tissue. Forty-seven of the subjects, or 39 per cent, gave a history of excessive colds and seventy-two, or 59 per cent, gave a history of severe tonsillitis. On culture, beta hemolytic streptococci were recovered from the throat in 30.9 per cent and from the nasopharynx in 14.6 per cent.

DISCUSSION

Abnormal lymphoid tissue in the upper respiratory tract is easily infected. It provides the point of entry for the majority of upper respiratory infections. This is especially true in the nasopharynx. The recurrence of rheumatic fever is more or less directly related to the incidence of upper respiratory infection. Schlesinger¹ states "It is no exaggeration to say that acute nasopharyngeal infection is the most serious menace to the rheumatic child with heart disease. . . . Relapses unpreceded by throat infections have been rare. . . . The problem is centered in the pharynx. It seems that if outbreaks of throat infection could be avoided relapses would practically never occur." The same writer emphasizes the mild character of the throat infection and the quiescent period of seven to twenty-one days that ensues before the relapse of rheumatic fever. He further states that such infections are frequently overlooked as the cause of the relapse.

The rheumatic fever patients examined in this study exhibited an unusually high incidence of abnormal nasopharyngeal lymphoid tissue. This condition was present in 48.8 per cent of the convalescent group. The danger of relapse in these individuals is obviously greater than in those with a normal nasopharynx. The nasopharynx is frequently neglected as a site of infection. Inspection of the oropharynx often gives no clue to the presence of nasopharyngeal disease. Severe acute infection may be lurking above the palate only to be revealed by the postnasal mirror and nasopharyngoscope. The presence of this tissue also appears to bear some relationship to the prolonged activity of rheumatic fever. Of these patients showing active rheumatism, 74.8 per cent had abnormal nasopharyngeal findings. Attention to this area early in the disease might greatly shorten the period of hospitalization and disability. Robey and Finland,² reporting 165 patients upon whom tonsillectomy was performed, state "The earlier the focus of infection

is discovered, the greater the possibility of lessening the recurrence of attacks the length of time in the hospital and danger of cardiac involvement."

TREATMENT

This survey does not include the actual treatment of any of these patients, however, the indications and type of treatment recommended were recorded in each instance at the time of examination. Such recommendations were based on otorhinolaryngologic evaluation and with full recognition of the presence of rheumatic disease.

The question of tonsillectomy is one of great controversy and has been the subject of extensive debate. Medical literature affords ample testimony to support anyone's personal views. The greatest amount of literature deals with the problem in early childhood. Certainly, in adults in whom the history and examination show the presence of diseased tonsils the operation is indicated and should be done as soon as the possibility of precipitating a relapse is past. The removal of tonsils alone is not enough. The problem is only partially solved if diseased lymphoid tissue is allowed to remain in the nasopharynx. Perhaps it is because of this that tonsillectomy in rheumatic fever has been the subject of so much controversy and has proved to be a disappointment in so many instances.

Infections of the oronasal lymphoid tissue, when bacterial cultures reveal susceptible organisms, may be eliminated or neutralized by chemotherapy and the use of penicillin before operation and during the postoperative period, thereby obviating the dissemination of such infection by operative trauma. In a small series of patients convalescent from acute exudative nasopharyngitis caused by beta hemolytic streptococci, in whom repeated nasopharyngeal cultures were positive, by the use of penicillin nose spray (1000 units per cc., three times daily) it was possible to eliminate surface organisms for four to five days. Cultures became positive again when the spray was discontinued. This, of course, demonstrates the need for a parenteral concentration of penicillin to eliminate organisms within infected tissues. The topical use of antibiotics alone is not considered adequate to combat infection.

The treatment of abnormal lymphoid tissue in the nasopharynx, if large in amount, is surgical removal supplemented by the use of radium by Crowe's method.³ Smaller amounts may be treated by radium alone. The nasopharyngeal radium applicator offers a safe method for removing this tissue with a minimum of local disturbance. Since the only contraindication to the use of radium would be the presence of acute infection in the pharynx, irradiation of the nasopharynx may be started early in the course of the rheumatic attack. The beneficial effect of irradiation on subacute and chronic infections is well recognized.

CONCLUSIONS

1 Two hundred and fourteen patients in various stages of acute rheumatic fever were examined with reference to abnormal oronasal lymphoid tissue. An unusually high incidence of abnormal oronasal lymphoid tissue was found in these patients.

2 Abnormal oronasal lymphoid tissue seems to bear a direct relationship to the prolonged course of rheumatic disease and the possibility of recurrent attacks.

3 The proper removal of this tissue would appear to lessen the possibility of recurrence of the rheumatic fever and shorten the course of the disease.

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THE PROBLEM OF DOSAGE IN THE ADMINISTRATION OF GOLD SALTS FOR RHEUMATOID ARTHRITIS

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THE various salts of gold have met with considerable favor in the treatment of rheumatoid arthritis and undoubtedly would be even more popular but for the rather high prevalence of toxic reactions which accompany their administration. Approximately 25 per cent of patients who are treated with gold salts sooner or later develop a skin rash or some other form of gold intoxication such as stomatitis or gastrointestinal symptoms. The gold rash usually takes the form of small patches of squamous dermatitis, but occasionally an extensive and stubborn exfoliative dermatitis is encountered. Gastrointestinal symptoms are usually mild and evanescent, but rare instances of fatal ulcerative enterocolitis have been reported. Depression of the bone marrow is occasionally observed, manifesting itself as a purpura, leukopenia or aplastic anemia. The purpura is usually of the simple variety, but in rare instances thrombocytopenic purpura has developed with often disastrous results. Leukopenia is an unusual occurrence and usually disappears with the discontinuation of gold. Cases of true agranulocytosis have been extremely rare. A few cases of acute glomerular nephritis have followed the use of gold and toxic hepatitis is an infrequent sequel.

While it is true that the incidence of gold reactions has been rather high, most of them have been of a mild character. However, the occasional severe and even fatal reaction has caused many physicians to be extremely apprehensive about the use of these drugs. Some in fact refuse to use gold salts under any circumstances.

Gold, like all heavy metals is a poisonous element. This has been repeatedly demonstrated by experiments on animals where large doses administered either by mouth or intravenously produce destructive and fatal lesions in the liver and kidneys. However, the toxicity of gold, like that of other heavy metallic salts is dependent upon the dosage employed. The problem with gold therapy as in the case of the arsenicals has been to determine the dosage which while not producing toxic reactions, would still be therapeutically effective.

LARGE DOSAGES ADVOCATED BY THE EARLIER INVESTIGATORS

Unfortunately for the reputation of gold therapy, the earlier investigators had no method of estimating the proper dosage for the human

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being As a result, the doses administered were far too large for safety For instance, one of the first gold salts to be administered clinically was gold sodium thiosulfate (sanocrysin), which was first introduced by Mollgaard¹ in 1924 This investigator first used sanocrysin extensively on patients with pulmonary tuberculosis The doses which Mollgaard employed were enormous, compared with present standards He started with 10 mg of the salt and gradually worked up to a 1000 mg dose In other words, *one dose* was equivalent to the total amount of gold now given for a course of several months duration!

In 1932 Secher² of Copenhagen reported a small series of thirty-two cases of chronic arthritis which he had treated quite successfully with sanocrysin This writer also used massive doses of gold salts, beginning with 250 mg and concluding with 750 to 1000 mg in a single dose The interval between doses was only three to four days In the same year Faber³ reported his results with sanocrysin in the treatment of pulmonary tuberculosis and chronic polyarthritis In the case of the arthritic patients he began with 100 to 150 mg, gradually increasing the dose to a total of 600 mg per week Two out of seven patients treated developed a skin rash

To Jacques Forestier⁴ the major credit must go for the first careful studies on the use of gold salts in rheumatoid arthritis After several preliminary reports he published an article in the *Lancet* in 1934 in which he recommended sodium aurothiomalate (myochrysine) and aurothioglucose (solganol-B) as the more desirable agents for use in the treatment of arthritis The dosage recommended for myochrysine was 100 to 200 mg injected weekly The total amount for one series was 1.5 to 2 gm Several series were advised, with intervals of six to eight weeks between series Forestier stated that much larger doses had been given in certain cases, but were not recommended as a routine by anyone with limited experience with gold compounds

In 1935 Forestier⁵ reported on six years' experience with gold salts in the treatment of rheumatoid arthritis By this time he had decreased his individual doses from a maximum of 200 mg to weekly doses of 100 mg, the total dosage ranging as previously from 1500 to 2000 mg Forestier felt that solganol-B could be used in much higher doses than any of the gold salts previously employed Starting with an initial dose of 50 mg, he increased the weekly dose up to 200 and sometimes 300 mg, the total amount for the series ranging between 2500 and 3000 mg This was surprising in view of the fact that most modern authors consider solganol and myochrysine equally toxic, and with some reason, for they contain equal quantities of metallic gold In this report Forestier stressed the importance of giving gold salts in a series of courses which were to be separated by rest periods of six to eight weeks In the series of 500 cases treated with gold salts Forestier reported four cases of intoxication, two of agranulocytosis and two of thrombocytopenic purpura One of the patients died

About this time Hartfall and Garland⁶ made their first report from England on their results with gold salts in rheumatoid arthritis. These authors used all three of the more popular gold salts—gold sodium thiosulfate, myochrysine and solganol B. The maximum single dose was 200 mg. at weekly intervals. In this series of 100 cases, marked improvement was noted in 70 per cent of the cases, but three of the patients died from gold intoxication, one from agranulocytosis, and two from thrombocytopenic purpura.

Pemberton,⁷ whose report appeared in 1935, favored large doses of gold salts, advocating doses of 250 to 500 mg. up to a total of 1500 to 3000 mg. for the whole series. Pemberton ran into all of the usual toxic reactions which is not surprising in view of the large dosage employed. He maintains, however, that the dose of gold used does not bear much relation to the toxic manifestations, which may come out either early or late in the course of treatment. There is some basis for this point of view as I shall point out later.

THE RECENT TREND TOWARD SMALLER DOSAGE

In 1936 came the first reduction in dosage. Hartfall and Garland,⁸ in view of the three fatalities which they had sustained in their first series of 100 cases, reduced their maximum dose to 100 mg., with a total dosage of 1000 mg. for each series. Furthermore, the interval between courses was lengthened to three months. On this reduced dosage they found toxic reactions still common, but definitely reduced both as regards frequency and severity. Moreover, reduction in dosage was achieved without any sacrifice of therapeutic results. These investigators also found that there was no difference in the incidence of toxic reactions between intravenous and intramuscular therapy. Hartfall and his collaborators⁹ made a complete study of 750 cases of rheumatoid arthritis and again concluded that the maximum single dose of gold salt should not be more than 100 mg. However, they did feel that their earlier experience indicated that larger doses produce more striking results. In this large series of cases, 80 per cent showed cure or striking improvement.

Following this important study by Hartfall and his co-workers, the 100 mg. dose became the standard for gold treatment. It was used by Copeman and Tegner¹⁰ and the earlier American writers, such as Dawson, Boots and Tyson.¹¹ Cecil Kammerer and de Prume,¹² and others. Ellman and Lawrence,¹³ in 1938 made an interesting study in which they compared the results obtained with large and with small doses of gold. In the first series a maximum dose of 200 mg. was used to a total dosage of 2500 mg. In the second series the maximum dose was 100 mg. A third series of controls received injections of sterile oil. The number of cases in each group was too small to be very convincing. However, in a series of sixteen patients who received the large doses, fifteen or more than 90 per cent were either cured or improved, wh-

in the series that received the smaller doses, fourteen out of sixteen were either cured or improved. In the control series of twenty cases, only one patient made a complete recovery, thirteen were improved. The effect on the sedimentation rate was striking for both the large dose series and the small dose series. In this limited series the results appeared to be just about as good with small doses as with large doses. The authors felt very strongly that after the sedimentation rate reached normal, only small doses of gold should be employed. In this small series of cases one of the patients receiving the large doses died of thrombocytopenic purpura.

Up to this point the treatment of rheumatoid arthritis with gold salts had been purely empirical and the dosage employed was equally so. However, in 1941 Freyberg¹⁴ and his co-workers undertook a study of the metabolism and excretion of gold compounds in arthritic patients treated with gold salts in an effort to put gold therapy on a more rational basis. These authors found that when gold salts were administered either intravenously or intramuscularly to animals, the gold was absorbed into the blood stream and deposited in various organs, especially the liver, spleen, lymph nodes and bone marrow. They found that the excretion of gold in the feces was rather irregular, but larger amounts of gold were eliminated in the feces when larger amounts of gold were injected. Gold was excreted chiefly in the urine. It was always observed that on the day of injection larger amounts of gold were eliminated than on other days, and that the amount in the urine increased in step like fashion, similar to the blood concentration. It was evident therefore that this soluble gold was quickly absorbed from the site of injection and that increasing amounts of gold arrived at the kidneys to increase the urinary excretion of gold. The amount of gold in the plasma remained relatively constant between weekly injections, hence the larger amount in the urine on the days of injection did not result from a significantly higher plasma gold content on that day compared to subsequent days.

According to Freyberg, large amounts of gold were retained during the period of its administration, regardless of which of the gold salts was employed. A great deal more gold was retained than was excreted through the kidneys. In two patients who were treated each with weekly doses of 100 mg. of gold sodium thiomalate (myochrysine) over a period of thirty-nine days, the amount of gold retained in the body was found to be 81 and 86 per cent respectively of the amount injected. This retained gold continued to be excreted for long periods of time. Gold was found in some cases in the blood and urine as long as a year after treatment was stopped.

An interesting and important practical feature of Freyberg's study was that although patients who received only 50 mg. of gold salt weekly had a total dosage comparable to the group that were given 100 mg. weekly, those who had the smaller doses ceased to excrete the gold

after a period of only three to four months following the cessation of treatment

Freyberg concluded from these studies that, in the past, unnecessarily large amounts of gold salts had been injected weekly. He proposed therefore a still further reduction in the weekly dose of gold salt, namely 50 mg. instead of the 100 mg. dose which was being used at that time.

Since the publication of Freyberg's studies the general trend, particularly in this country, has been to adopt the 50 mg. dose of gold salts for routine treatment. For example, in a report by Hartung¹⁵ in 1943 the author recommends the 50 mg. dose of gold salt. In a recent personal communication Hartung says that instead of the weekly injection of 50 mg. he is now trying a 25 mg. dose twice a week. Some writers, such as Cohen and Dubbs¹⁶ and Price and Leichtentritt,¹⁷ still adhere to the 100 mg. dose. Other physicians vary the dose according to the patient, severity of the arthritis, and so forth. Recently Rawls¹⁸ and his associates have reduced the dose of gold salts still more markedly. His standard schedule is 5 mg. intramuscularly once a week for three weeks, 10 mg. intramuscularly once a week for three weeks, and then 25 mg. once a week.

From this brief survey of the literature it is obvious that the original doses of gold salts employed by the early workers were much too high. The first reduction in dosage by Hartfall and Garland resulted from their high incidence of fatalities. A still later reduction by Freyberg came about from his discovery that 75 or 80 per cent of metallic gold was retained in the system when 100 mg. doses of gold salts were administered weekly. There are some who still feel that the large doses produce better clinical results, but in the opinion of the writer such doses are rarely justified in view of the dangerous reactions which they may induce. I suspect that the still smaller dose (25 mg. per week) is too small for an active case of rheumatoid arthritis. It might be adequate for some of the very mild cases.

METHOD EMPLOYED AT THE NEW YORK HOSPITAL

In the Arthritis Clinic of the New York Hospital our method of administering gold is as follows. The first injection of myochrysine or solganol B consists of 10 mg. injected intramuscularly with a long needle into the buttock. The second dose, one week later, is usually 25 mg., though if there is any question of drug idiosyncrasy, the 10 mg. dose is repeated. The third injection one week later consists of 50 mg. of gold salts. The 50 mg. dose is then repeated at weekly intervals until the patient's symptoms are relieved and the sedimentation rate has reached normal. If any gold reactions occur, gold therapy is immediately discontinued. In exceptional cases all very mild rheumatoid arthritis or any patients who are suspected of being susceptible to the drug, the maximum dose is 25 mg. once a week. We much

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TOXIC HEPATITIS DURING GOLD SALTS THERAPY: ITS EFFECT ON THE COURSE OF THE RHEUMATOID ARTHRITIS

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THE development of jaundice in patients with rheumatoid arthritis has been observed to have beneficial effects on the course of the arthritis. We were interested to observe the changes which took place in four cases of this type which came under our own observation. These four subjects had received gold salts as part of their therapy, and it was presumed, though not proved, that the intercurrent hepatitis was caused by the gold salts.

The mechanism of action of gold salts in rheumatoid arthritis is still unexplained, although it is conceded by most authorities who have had extensive experience in gold salts therapy that it produces an arrest of the disease in at least 50 per cent of the cases in which it is properly applied. One theory as to its mechanism is that it produces its beneficial effects through its toxic action on the liver. We are interested to see whether or not our four cases tend to support this theory.

The literature also suggests that intercurrent jaundice may have ameliorating effects on rheumatic pain in general, whether or not due to rheumatoid arthritis, and also on allergic states, but these phases of the subject are beyond the scope of the cases reported here.

LITERATURE

In 1933 Hench¹ reported intercurrent jaundice in sixteen patients suffering with chronic infectious arthritis, primary fibrositis or sciatica. In some cases the jaundice developed without known cause, in others following and presumably caused by the administration of drugs such as cinchopen. Hench reported the development of remissions in fourteen of the patients. Similar observations were made the following year by Sidel and Abrams.²

In 1937 Boros³ reported a case of hay fever, asthma and "rheumatic pain" all of which cleared up with the onset of an intercurrent jaundice. Whether or not this jaundice was related to the intake of cinchopen the author could not be certain. Boros' observations as well as those of Hench, in observing that the remissions occur not only in atrophic arthritis but also in unrelated conditions as sciatica, seemed to imply that the jaundice was nonspecific in effect, producing an analgesia in general and/or possibly an anti-allergic action.

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In 1938 Hench^{4, 5} reported nineteen further instances of remissions occurring during the course of atrophic arthritis and nine during the course of primary fibrositis, following the advent of jaundice. He also reported four cases of atrophic arthritis and nine cases of other forms of rheumatism, which were not relieved by intercurrent jaundice. Hench believed that the jaundice had to be more than mild in order to produce this beneficial effect, or above 8 mg of bilirubin per 100 cc of serum. Lichtman⁶ supported Hench's observations as to the ameliorating effect of jaundice in rheumatoid arthritis and observed that as in his case the disease could be of long standing (ten years) and still be beneficially affected.

The cause of the jaundice, according to Hench, made no difference in its effect on the rheumatism. However, Hartfall, Garland and Goldie⁷ in reporting eighty-five cases of "gold jaundice" observed no beneficial effect from jaundice due presumably to this cause. Their high incidence of jaundice (9.6 per cent) makes one suspect something other than the gold therapy as the cause of the jaundice. They stated specifically that those with jaundice were worse than those who did not experience this complication. On the other hand, Cecil⁸ noted a "temporary cure" following jaundice which developed during gold salts administration.

FOUR CASE HISTORIES

Below are recorded four case histories of patients with rheumatoid arthritis who developed intercurrent jaundice. All four patients had received gold salts but only two received this type of therapy while under our direction. The other two came to us from other clinics for treatment of their jaundice. We have treated personally, or had under our direct supervision, 800 patients with rheumatoid arthritis who received gold salts therapy. The incidence of jaundice in our series, therefore, was two in 800, or 0.25 per cent.

CASE I—M M., a man aged 60, who had had rheumatoid arthritis for five years, was admitted to the hospital on January 4, 1941. Gold salts in the form of gold calcium thiomalate were started on January 26. Its administration was continued through May 16 of the same year, by which date a total of 2000 mg of gold salts had been given. The initial sedimentation rate was 105 mm per hour (Westergren). By May 8 the sedimentation rate was still elevated, being 62 mm per hour, but on May 15 it suddenly dropped to 25 mm per hour. The following day another injection of gold salts was given which proved to be the last, because on May 19 the presence of icterus was noted. The icterus index on that day was 57. On the same day the serum bilirubin was 15.6. The icterus index rose to a maximum of 107 by the 26th of the month. Subsequently, the icterus index as well as the serum bilirubin gradually returned toward normal but as the jaundice receded the sedimentation rate rapidly rose so that by June 23 the sedimentation rate reached 115 mm per hour. Other pertinent data are indicated in the table and graph (Table 1, Fig. 77).

It is particularly interesting to note that the sedimentation rate rapidly returned toward normal just preceding and during jaundice, but rose again as the jaundice receded.

With the onset of jaundice the patient felt symptomatically better. There was some recession in the objective findings in the joints such as decreased fluid and

TABLE 1—COURSE IN CASE I

Date	Remarks	Sed Rate	Icterus Index	Alkaline Phosphatase	Hanger Test
1941					
Jan. 4	Admitted to hospital				
6		105			
14		90			
22		74			
26	Gold salts started				
28		70			
30		69			
Feb. 6		62			
14		60			
20		52			
March 12		58			
20		52			
April 1		65			
2		73			
19		79			
May 2		55			
8		62			
15		25			
16	Last dose of gold salts				
19	Icterus noted		57		
21	Fibrinogen 0.3				
22		16			
23	Total cholesterol 90 Esters 45 Ratio 50				
26		24	107	12 7	
26	Serum bilirubin 15 6				
28			79	12 7	4 plus
28	Serum bilirubin 8 7				
29		31			
June 2			37		
5		68			
9			26	7 2	4 plus
10	Icterus clearing				
16		36		6 5	
16	Urine urobilin 144				
23		115			
July 25		101			

periarticular swelling but these effects were far from dramatic and by June 23 the patient was worse than before the jaundice developed. The subsequent course during the next few years was downhill.

CASE II.—J B a man aged 60 who had suffered from rheumatoid arthritis for one year was first seen by us on September 6, 1944. His sedimentation rate on

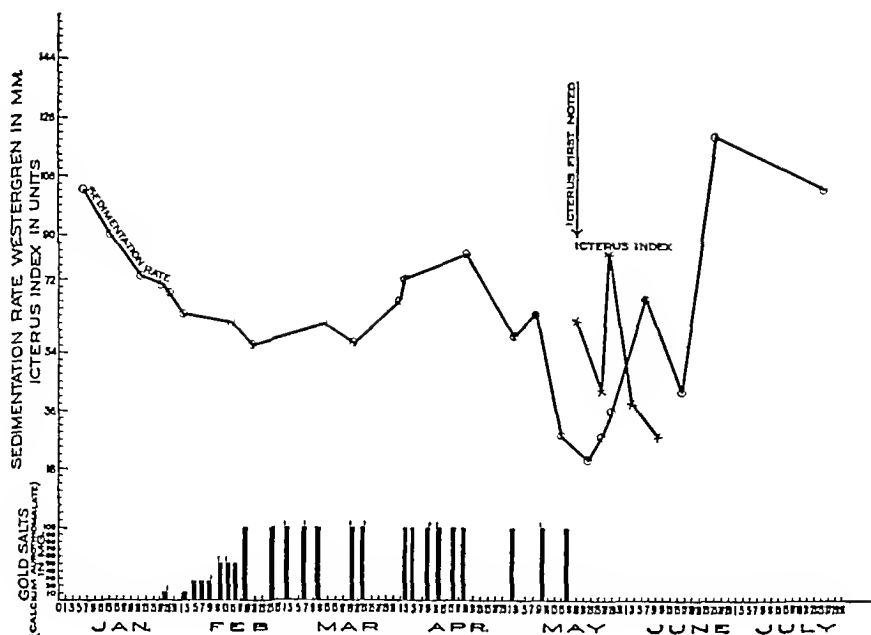


Fig 77 (Case I)

that date was 110 mm per hour. He was immediately admitted to the hospital and on the same date gold salts in the form of Solganol-B were started. He received 25 mg twice a week for two months and thereafter 25 mg once a week until April 2. This proved to be his last dose because on April 5 jaundice was noted.

After admission the sedimentation rate came down slowly so that by December

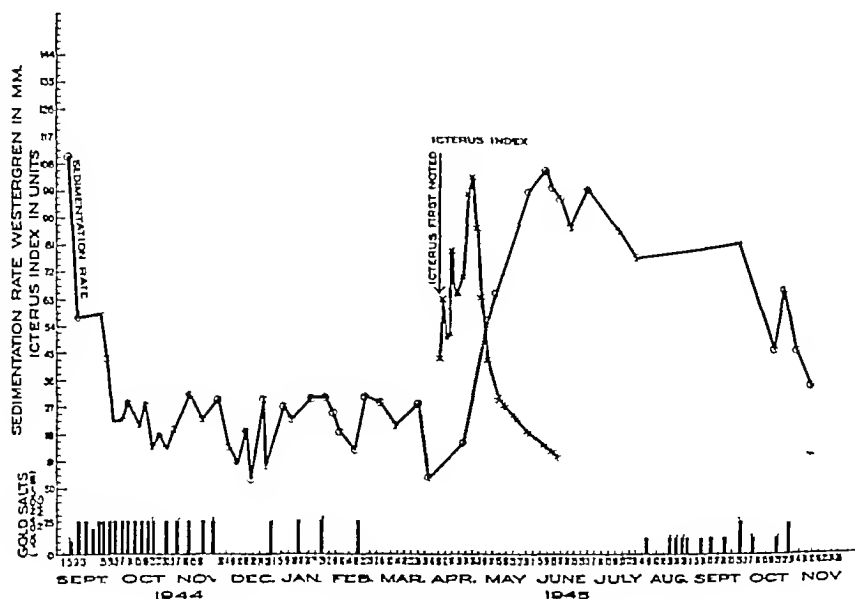


Fig 78 (Case II)

18 it was 4 mm per hour and then after a temporary rise came down to 5 mm on April 2, a few days before the icterus was noted. The icterus index on April 8 was 41 and gradually rose to 103 by April 27 between which dates the sedimentation rate remained within normal limits.

As the icterus receded the sedimentation rate again rose to a maximum of 106 mm on June 8 by which time all the jaundice had disappeared (see Table 2 and Fig 78) By April 2, before the onset of jaundice, the patient had experienced a

TABLE 2 — COURSE IN CASE II

Date	Sed Rate	Date	Sed Rate	Icterus Index
1944				
Sept. 6	110	March 5	28	
6	Admitted to hospital	12	20	
6	Gold salts started	26	28	
11	57	April 2	5	
23	58	April 2	Last gold salts injection	
27	42	April 5	Icterus first noticed	
Oct. 2	22			41 5
4	22			63 4
9	29			50 1
11	26			51 5
16	20			78 1
19	28			68 7
23	14			63 4
26	18			71 7
30	13		14	
Nov 3	20			97 3
13	31			103 1
20	22			86 8
29	30			63 7
Dec. 5	13	May 3		43 4
10	8	7	56	28 9
14	19	14	65	27 0
18	4	17		21 2
26	30	23		20 6
27	8	24		18
1945		31	98	
Jan. 5	27	June 1	Discharged from hospital	
12	22	8	106	15
22	30	11	100	11 3
29	30	14	96	10 2
Feb 5	25	21	85	
8	19	July 2	100	
16	12	19	84	
23	30	30	75	
		Sept. 10	80	

complete remission of his rheumatoid arthritis. All the joints were normal in appearance as well as in function. This remission persisted through the duration of the jaundice, but as the jaundice subsided, and as the sedimentation rate rose the patient's rheumatic symptom returned so that on discharge from the hospital on June 1 he had as much arthritis as when he entered the hospital on September 6. In this case the patient was apparently completely well when the jaundice started and developed a marked relapse immediately subsequent to the jaundice.

TABLE 3—COURSE IN CASE III

Date	Remarks	Sed Rate	Icterus Index	Hanger Test	Cholesterol	Esters	Ratio
March 2	Gold salts—first dose	73	.				
	Solganol B, 25 mg						
9	Second dose—Solganol B, 25 mg						
16	Third dose—Solganol B, 25 mg						
23	Jaundice first noticed	55	136	4 plus	185	45	24
25	Admitted to hospital						
26	Serum bilirubin 17.4						
26							
29		54					
April 1		42	125	4 plus	210	40	19
2							
7	Skin rash	42	115		180	40	22
8							
12							
15							
21		42	125	4 plus	210	35	16
22		50					
22			115 4	4 plus	160	40	25
29		60	68 2		180	90	50
May 7		58		4 plus			
7			46				
8	Discharged						

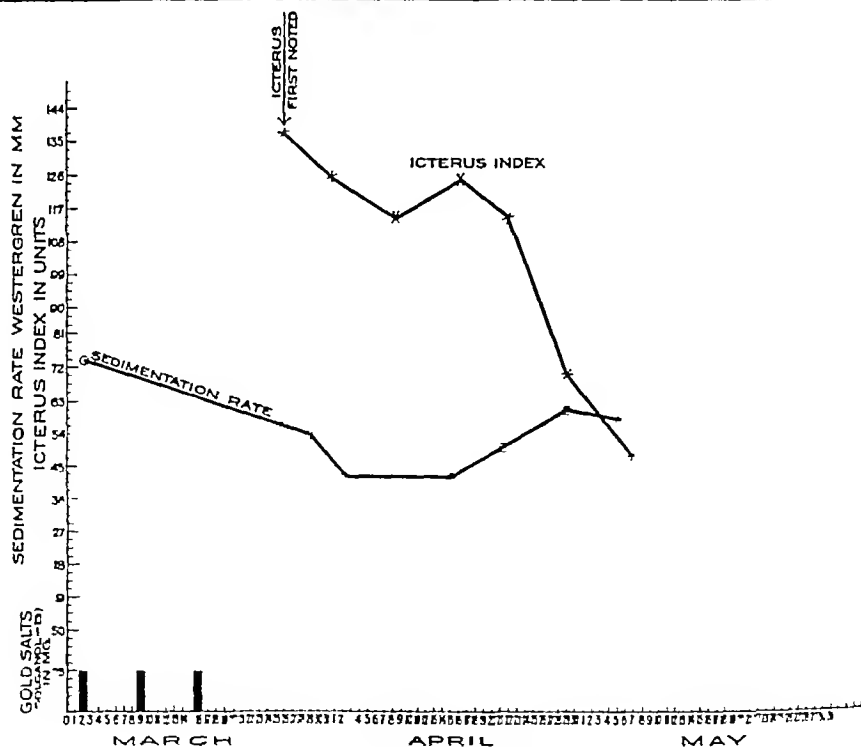


Fig 79 (Case III)

CASE III—H.P., a woman aged 36 had had rheumatoid arthritis for five years. On March 2, 1943 she received 25 mg of Solganol B and on March 9 and 16 a similar dose, all at another clinic. At the beginning of this therapy the sedimentation rate was 73 mm per hour. On March 23 icterus was first noted and on March 25 she came to our clinic for the treatment of the jaundice and was admitted to the hospital. By March 26 the serum bilirubin was 17.4 mg per 100 cc the sedimentation rate 55 mm per hour and the icterus index 130. Other pertinent data are noted on Table 3 and Figure 70. The icterus persisted through March 22 and subsequently began to recede so that by May 7 it was 46 units. The patient was discharged on the following day.

In this case the sedimentation rate was somewhat lower during the jaundice but did not fall precipitously as in the other two cases above.

During the jaundice the patient was symptomatically better but far from well. There was somewhat less pain and swelling of the joints but the joints were in no sense free of active rheumatic manifestations. After the patient was discharged from the hospital, she remained somewhat better symptomatically for a few months and then returned to approximately the state she was in when gold salts were first begun on March 2.

The follow-up study two and a half years later showed that the patient was still suffering with active rheumatoid arthritis the condition remaining about the same as when first observed in this study.

CASE IV—E.N. a girl aged 10 had had rheumatoid arthritis (Still's disease) for eight years. The sedimentation rates for the eighteen months prior to the use of gold salts are recorded in Table 4. Between April 27 and June 6 1945 the

TABLE 4—COURSE IN CASE IV

Date	Sed. Rate	Icterus Index	Hanger Test	Total Cholesterol	Esters	Ratio
1944						
Jan. 26	83					
Nov. 12	82					
1945						
Jan. 24	75					
Feb. 12	64					
March 14	64					
April 12	70					
18	70					
27	First dose of gold salts					
June 6	Last dose of gold salts					
	Total to date 95 mg					
13	Admitted to hospital					
14	100	33.2	3 plus	420		
15				360		
19	10	30.0				
27		12.5				
28	Discharged from hospital					
July 11	"Jaundice all cleared"					
Sept. 2	29	7.5	2 plus			

hour and the icterus index 33.2 units. On June 19 the sedimentation rate had dropped to 10 mm per hour, the icterus index remaining about stationary. By July 11 the jaundice was not visible clinically. During the jaundice the patient was slightly, though hardly perceptibly, better in that the objective signs of actual arthritis were fewer. However, this amelioration was short lived, and a recent follow-up report found the patient unimproved.

COMMENT

It is interesting to observe that the initial sedimentation rate of many patients with rheumatoid arthritis who are admitted to the hospital falls rapidly within the first few days of hospitalization, and before any form of therapy has been instituted. The reason for this is not clear, but should be kept in mind in evaluating any form of therapy when using the sedimentation rate as a yardstick.

Attention is called to the fact that in two of these patients the sedimentation rate fell precipitously just before the development of jaundice. This phenomenon has been observed in other situations in which the function of the liver is embarrassed, such as at the onset of chronic passive congestion of the liver in acute rheumatic fever subjects who develop cardiac decompensation. It should be pointed out that such a sudden drop, in a patient with rheumatoid arthritis, rather than being considered a beneficial sign should place the physician on his guard for an impending liver catastrophe.

It can be stated that in at least two of the subjects whose cases are described above the icterus resulted in a remission of symptoms, though this remission was extremely temporary. In one case (J. B.) the patient was much worse following the jaundice than he was before its onset. Since all these four cases may be considered instances of failure with gold salts therapy in rheumatoid arthritis, this study certainly lends no support to the theory that gold salts produce their beneficial effect by liver damage.

It is purely an assumption that the icterus which developed in the cases described in this report was due to gold salts. The incidence in our own series of two cases in 800 subjects is so low that it can be argued that these subjects would have developed icterus under any condition since idiopathic jaundice is fairly common in any group of subjects throughout the general population.

SUMMARY AND CONCLUSIONS

1. Jaundice is an uncommon sequela of gold salts therapy (two in 800 cases).

2. In two of the cases here reported, visible jaundice was preceded by a few days by a marked drop in the erythrocyte sedimentation rate. In the other two cases the sedimentation rate dropped as the jaundice increased.

3. The reduction in the sedimentation rate was temporary and the

sedimentation rate started to rise about the same time the jaundice started to recede

4. The onset of the jaundice was accompanied by an improvement in the patient's subjective and objective symptoms

5 This clinical improvement was temporary, all four cases here reported relapsing almost immediately after the jaundice subsided

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PERICARDIAL EFFUSION IN RHEUMATOID ARTHRITIS

LOUIS W GRANIRER, M D °

It was thought at one time that the heart was rarely affected in rheumatoid arthritis. This concept was due mainly to the lack of complete clinicopathologic studies. Although the electrocardiographic examination is generally of little or no help, careful physical examination may reveal some evidence of permanent cardiac involvement.¹ This finding has been borne out recently by postmortem examinations showing an unusually high incidence of heart disease in rheumatoid arthritis.

Young and Schwedel,² for instance, in 1944 reported thirty-three cardiac lesions in thirty-eight cases of rheumatoid arthritis that came to autopsy. The lesions were not due to arteriosclerosis or to hypertension. Only three cases gave a frank history of rheumatic fever in childhood.

In 1941, Baggenstoss and Rosenberg³ studied the clinical records and autopsies in thirty cases of rheumatoid arthritis with progressive polyarticular inflammation. Fifty-three per cent had rheumatic heart disease and 33 per cent had a low grade, nonspecific glomerulonephritis. Boas and Rifkin⁴ in 1942 reviewed eighty cases of rheumatoid arthritis and found valvular heart disease in more than 17 per cent.

The patient that we are presenting had rheumatoid arthritis according to the classification based on the clinical, laboratory and radiographic observations as defined by the American Rheumatism Association.⁵ He had an inflammatory polyarticular process which was progressive and deforming.

J S., a white man, 44 years old, had had no childhood illness including scarlet fever. There was no history of rheumatic fever in his youth and there had been no arthritis in the family. He had developed a severe sore throat two years before admission, following which he began to lose weight and to develop stiffness and pain in both knees and feet, hands and spine—especially in the sacroiliac areas. His appetite was poor and he was subject to "sweats." He had occasional traces of glycosuria and a rapid sedimentation rate. The pain and stiffness became more marked in the knees and spine and he was bedridden from time to time. We saw the patient first one month prior to the onset of acute illness.

His present illness began one day before admission to the hospital. He had a sudden onset of severe precordial pain associated with a slight cough.

On December 19, 1945, the patient was admitted to Rockaway Beach Hospital. *Physical examination* revealed an emaciated man of asthenic build (Fig 80, A and B). He showed the typical changes of rheumatoid arthritis in his hands and feet. He was cyanotic and complained of intense pain over the precordium. This

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was aggravated by coughing, deep breathing and change in position. He had pain, also in the right upper quadrant of the abdomen. The paroxysms of pain suggested a severe angina pectoris myocardial infarction or pleurisy. The neck veins were full and temporary cessation of breathing abolished the pain. He was pale and had flaring alae nasi. The temperature was 101° F pulse 120 and blood pressure 110/70.



Fig. 80—A Patient with pericardial effusion coexisting with rheumatoid arthritis.
B Same patient, lateral view

The heart was markedly enlarged in globular fashion. The apex impulse was visible. There was some impairment of the percussion note in the left axillary area. No evidence of consolidation could be found in the region of the left scapula. The heart sounds were rapid and slightly muffled. No murmurs could be heard. The electrocardiogram showed the S T segments elevated in Leads I and II (Fig. 81).

The abdomen was soft. Neither spleen nor liver was palpable.

The urine was negative. Hemoglobin was 89 per cent. The red blood cell count was 4,500,000. The white blood cells numbered 14,050 with polymorphonuclears 75 per cent and lymphocytes 24 per cent.

An x-ray examination of the chest showed no pericardial effusion and there was no abnormality of the lungs

A tentative diagnosis of pleuropericarditis was made and the patient was placed on a combined therapy of penicillin, 30,000 units given intramuscularly every three hours, and sulfadiazine, 15 gm every four hours. He responded poorly. The temperature was continuously elevated and he became more restless and sleepless in spite of sedation. Oxygen therapy increased his restlessness.

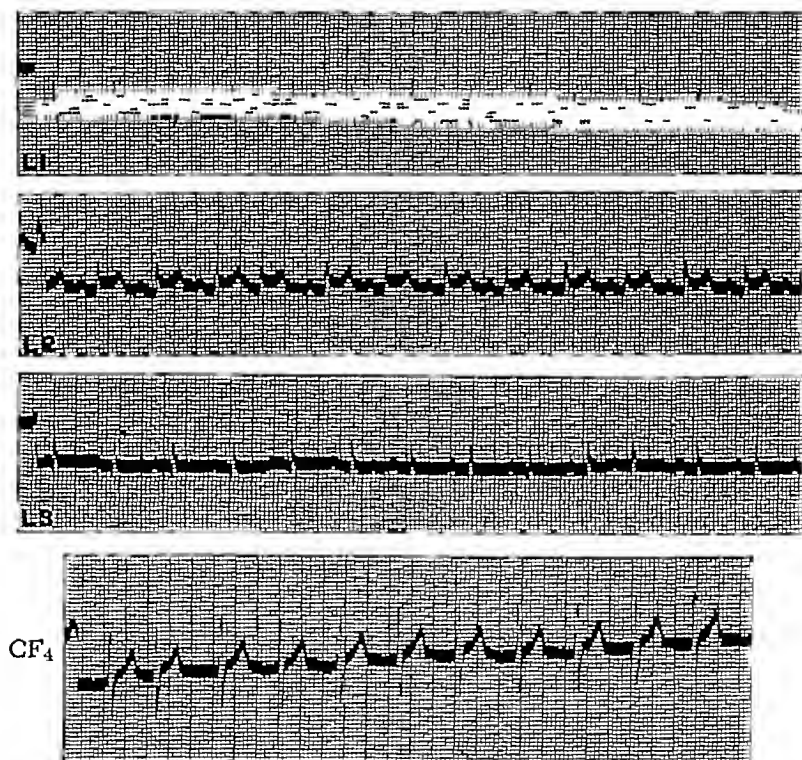


Fig 81—Electrocardiogram December 19, 1945. Leads I and II show elevated S-T segments (greater than 0.1 mm).

On December 23, 1945, the patient's red blood cells numbered 4,470,000 and his white blood cells 10,900 with 73 per cent polymorphonuclears. Blood culture was sterile after ninety-six hours' incubation. The sedimentation was 18 mm in thirty-six minutes (Cutler). His nonprotein nitrogen was 48.9 mg per 100 cc. of blood.

On the sixth day after admission (December 25, 1945) the patient showed a definite pulsus paradoxus. The apex impulse was not visible in the sitting or prone position. There was widening of the area of relative dullness in the first and second spaces to the left and right of the sternum in the recumbent position. There was an impaired percussion note in the left axilla and bronchial breathing (Ewart's sign) at the angle of the left scapula. The heart sounds at the apex were muffled. He was orthopneic and cyanotic. The blood pressure fell to 90/65. He showed all the signs of an acute cardiac tamponade and looked desperately ill.

A posterior pericardial paracentesis was done in the eighth left interspace in the center of the area of bronchial breathing, more towards the axilla than the



Fig 82.—X ray showing pericardial effusion before the chest was tapped

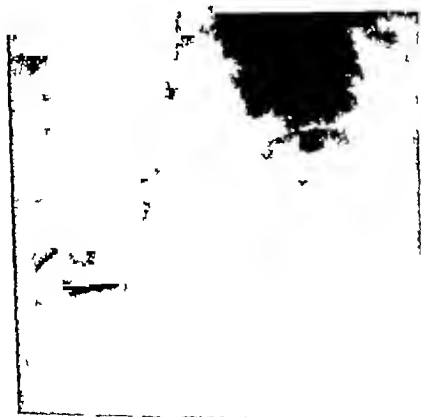


Fig 83—X ray forty-eight hours after the chest was tapped

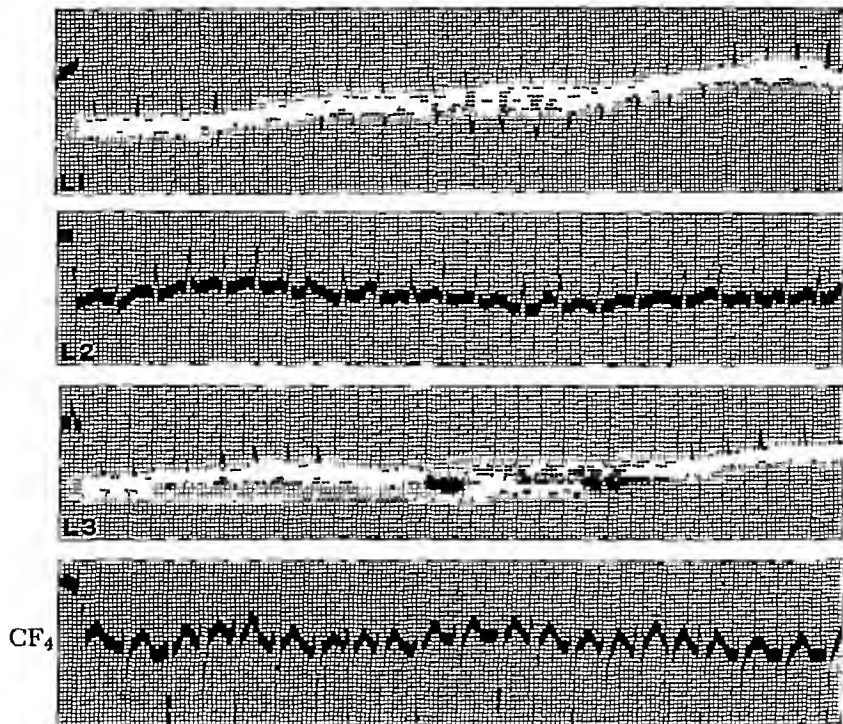


Fig 84—Electrocardiogram December 31, 1945 Auricular fibrillation with rapid ventricular rate

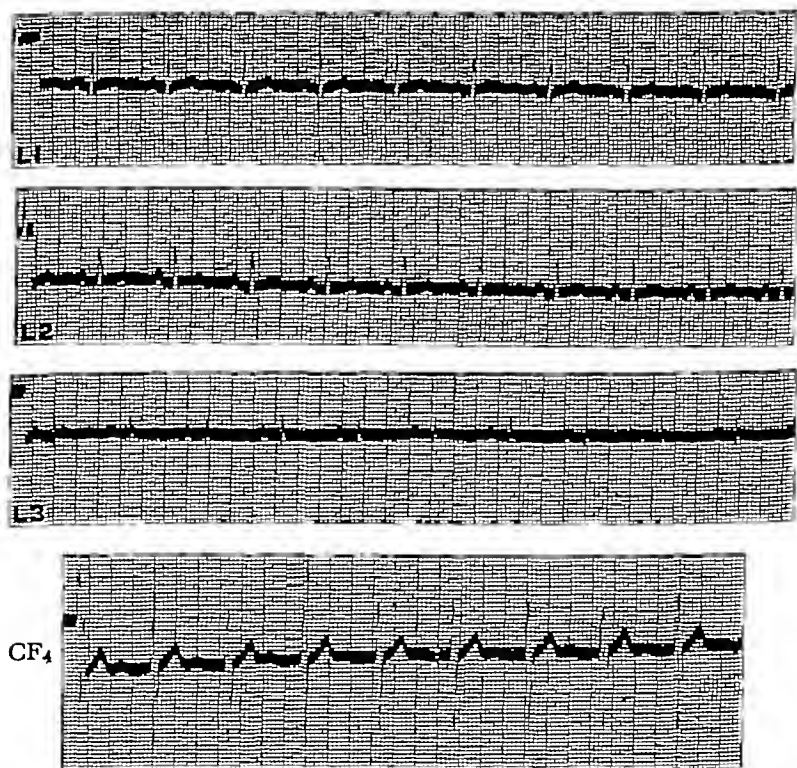


Fig 85—Electrocardiogram January 14, 1946 Low T waves in all leads, normal sinus rhythm.

spine. One liter of slightly turbid fluid was removed. Culture of this fluid was negative. Culture of the blood was also negative. It is interesting to note that the size and shape of the pericardial shadow changed only slightly until forty-eight hours after the aspiration of considerable fluid (Figs 82 and 83).

Sulfadiazine and penicillin were discontinued. It has been shown conclusively that these drugs aggravate an active rheumatic infection.⁶

The patient was now placed on 10 gm. of acetylsalicylic acid daily. His temperature dropped to normal within twenty-four hours. He then developed rapid auricular fibrillation (Fig 84), for which quinidine in large doses was ineffective. With digitalis, however, normal rhythm was restored (Fig 85). At this time he became incoherent, euphoric and complained of tinnitus. Salicylates were discontinued, after which he went on to complete recovery.

On January 15, 1940, his sedimentation rate was 18 mm. in thirty-six minutes.

On January 17, 1940, the uric acid in the blood was 2.3 mg. per 100 cc.

During the patient's stay in the hospital he had no joint symptoms. He was discharged on January 18, 1940, one month after admission.

A few days later there was a recurrence of the original picture of an active rheumatoid arthritis.

SUMMARY

A patient with rheumatoid arthritis, with no previous history of rheumatic fever, developed an acute pericarditis with massive effusion. There was no response to sulfadiazine or penicillin in adequate dosage. Pericardial paracentesis and salicylate therapy produced a rapid recovery. In the "rheumatic state" salicylates have a special effect on exudative lesions, such as pericarditis.⁷ There is a rapid absorption of exudate and diminution of fever.⁶

As in rheumatic fever, it is probable—judging from this and other reported cases—that every case of rheumatoid arthritis has some heart involvement, and that in a certain percentage there is a complete return to normal with the arrest of the disease. Unlike rheumatic fever, rheumatoid arthritis may spare neither heart nor joints.

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JUVENILE RHEUMATOID ARTHRITIS

(Still's Disease)

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STILL's disease has been described as a variety of chronic polyarthritis affecting children and marked by enlargement of lymph nodes, splenomegaly, and irregular fever. The term suggests a distinction between juvenile and adult rheumatoid arthritis which in practice we avoid. However, enough differences, related to age of onset, exist to make the separation practical as a means of classification.

Still¹ reviewed twenty-two cases of arthritis in children and felt that a small number of them were actually indistinguishable from adult rheumatoid arthritis, while a larger number (twelve of the twenty-two cases) were entirely different because of the characteristics noted above, and because there was less pain, an earlier onset, a lesser preponderance of females, and a liability to inflammation of serous membranes not shared by the rheumatoid arthritis of adults.

At present Still's disease is considered to be simply rheumatoid arthritis occurring in young individuals, the apparent differences are due to the varying effect of disease processes in youth and maturity. Several facts lend support to this impression. Lesions similar to those described in children, such as splenomegaly, lymphadenopathy, cardiac and pleuritic lesions, have also been reported in adults with rheumatoid arthritis.^{2 3} The age of onset is not a reliable index. It is very low in many cases of "adult type" of arthritis, and high, over 12 years even, in some cases that otherwise fit Still's pattern. Pathologic findings do not differ in youth or maturity except for certain skeletal changes to be mentioned later. In a large series the sex distribution is the same for juvenile and adult rheumatoids. Systemic reaction is less severe in adults, but this is true of most disease processes. Changes in various systems reported in adults suggest that inflammation of serous membranes and multiple system involvement are not confined to children. Subcutaneous nodules have been seen in any age group.⁴ Despite these discrepancies, and others unmentioned, it is convenient to consider Still's disease as rheumatoid arthritis beginning in children of the age of 12 years or less. We usually refer to these cases as juvenile rheumatoid arthritis.

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The sex distribution shows a female preponderance of five to one just as in adults.^{5 6} Still's disease may begin in children as young as 15 months of age, but in our experience the highest incidence is in those between the second and third years of life. It is not a common condition less than 5 per cent of all rheumatoids in our clinic fell into this group. Previous to an intensive study of Still's disease in this clinic, the percentage of rheumatoids below the age of 12 was only $1\frac{1}{2}$ which seems nearer the usual incidence.

PATHOLOGY

The pathologic findings are much as have been described in adult arthritis. Muscle atrophy, however, is more marked and bony lipping or spurring is rarely seen in children. Lymph node hyperplasia, splenomegaly and hepatomegaly are much more common in Still's disease (60, 30 and 23 per cent respectively in this clinic).

Myocardial, endocardial and pericardial lesions similar to those of rheumatic fever are occasionally seen in juvenile arthritis, adhesive pericarditis is a frequent finding in autopsy cases. Such lesions as well as the occurrence of pleurisy are fairly frequent in children.

The subcutaneous nodules seen in juvenile and adult arthritis are similar to those in rheumatic fever though grossly they may be larger.

Amyloidosis involving liver, spleen, lymph nodes and kidneys has been described as a complication of severe arthritis. It is rarely if ever noted in mild cases. In a fairly large series,⁷ over 20 per cent of patients developing amyloid disease were under the age of 12 years. Since this group comprises only about $1\frac{1}{2}$ per cent of all rheumatoids, amyloidosis appears most commonly to be a complication of the juvenile form of rheumatoid arthritis. It was present in one of two fatal cases in our series.

Relative to the skeletal system an interesting group of findings has been reported which results directly from arthritis and which is seen only when the disease begins in early life.⁸ Frequent descriptions have been given of a generalized lack of physical maturity without mental impairment, bird like facies and a delicate appearance of many arthritic children. Other than the generalized changes just noted, we have observed three types of localized skeletal change resulting from Still's disease, one or more of which are present in nearly 40 per cent of these patients. Twenty five per cent have an underdeveloped mandible (brachygnathia) which gives the so-called bird like facies. Thirteen per cent have luxation or fusion of two or more cervical vertebrae. About ten per cent have abnormal shortening of one or more fingers or toes. An occasional patient has shortening of an entire extremity. These changes occurred in normal individuals with no disturbances prior to the onset of arthritis. A past history particularly severe disease in those localized areas.

Fluid accumulates in joint spaces just as in adult rheumatoid arthritis and these accumulations are similar in all respects in those noted in the adult form of the disease

ETIOLOGY

The etiologic basis of Still's disease, as of adult rheumatoid arthritis, has not been determined. Certain predisposing factors common to patients of both age groups are

1 *Influence of climate* Arthritis is rare in the tropics and most common in temperate zones particularly if the region is fairly humid

2 *Season* Early spring and especially March brings the greatest number of recrudescences and new cases⁸

3 *Heredity* Thirty per cent of juvenile arthritics give a family history of rheumatic fever, arthritis, arthralgias, etc

4 *Constitutional factors* The children afflicted usually were not robust or vigorous even before the arthritis developed

Precipitating factors are

1 *Trauma* A history of recent injury may or may not be elicited. Injury may only serve to light up a pre-existing quiescent focus

2 *Infection* Recent upper respiratory infection, pharyngitis, tonsillitis, otitis or other localized infection is recorded in about 50 per cent of juvenile rheumatoid arthritis

3 *Operations* occasionally precede rheumatoid activity despite the fact that removal of definite foci of infection is a rational therapeutic measure

4 *Exanthematous infections*, such as scarlet fever or measles, occasionally seem to precipitate arthritis

Hemolytic streptococci (group and type not determined) have been obtained from the nose and throat of 60 per cent of patients studied bacteriologically in this clinic. This fact together with the high antistreptolysin titers obtained and the frequent association of an acute upper respiratory infection suggests a bacterial origin which cannot be dismissed without further study

X-RAY FINDINGS

Bony changes are not the earliest finding and a person may have definite arthritis without any significant changes manifest on x-ray films. There are four stigmas which may be demonstrated in rheumatoid arthritics⁹ regardless of age of onset

1 The earliest and most common finding is soft tissue change be it atrophy, swelling or effusion. Shadows of varying contour and density often enable the experienced observer to distinguish between swelling of tissue and effusion

2 Next in frequency is decalcification, a decrease in bone density without loss of form which may be local or generalized

3 Joint space narrowing or obliteration is seen only when the articular surfaces are damaged

4. Bone destruction, like the above change, is late in appearance. It consists of localized areas of loss of calcium seen on x ray plates as punched-out areas near epiphyseal lines

In addition to these general changes seen in patients of any age group, some features peculiar to juvenile rheumatoids have been observed

1 The previously mentioned growth changes (brachygnathia, brachydactylia and cervical fusion or luxation) are well demonstrated by x ray

2. Thickening of periosteum on the shaft of metacarpals or metatarsals and phalanges often gives a heavy appearance to these bones¹⁰

3 Thinning of the shaft of phalanges, etc., occasionally gives a delicate appearance quite opposite to the above

4. Accelerated growth of epiphyses may result in a disparity between the length of long bones

SYMPTOMATOLOGY

Three types of patients present themselves with juvenile rheumatoid arthritis. If the onset is insidious with no known preceding infection the child may complain of pain in a knee or ankle or begin to limp for no apparent reason. Afternoon temperature is normal or slightly elevated. Fatigue, anorexia and failure to gain weight may be noted. Pain in the joint increases and spreads to other joints. On examination there is frequently a tachycardia out of proportion to the low-grade fever. A soft systolic murmur may be heard which, without other symptoms, would be unimpressive. Moderate cervical, axillary, epitrochlear, inguinal or popliteal lymph node enlargement may exist. The spleen or liver may be enlarged. If the process is not recent, joint effusion and swelling together with local muscle atrophy present a striking picture. Fusiform swelling about proximal interphalangeal joints is seen. Terminal interphalangeal involvement is more common in Still's disease than in adult arthritis. As a rule, cases with such an onset are characteristic and easily diagnosed.

The second type of patient has a history of an acute onset of migratory polyarthritis often following some infection such as tonsillitis or pharyngitis. At first, joint involvement is minor but systemic reaction is marked with temperature fluctuating to 103° F or higher, a high erythrocyte sedimentation rate and marked leukocytosis. A distinct systolic murmur and an altered electrocardiogram pattern may exist, suggesting myocardial damage. These cases are easily confused with rheumatic fever, the diagnosis usually made on preliminary examination. Gradually the acute episode subsides, the temperature may continue elevated in the afternoon but at much lower levels. Now joint involvement becomes a prominent factor. Painful fusiform fingers and

joint fluid accumulations, muscular atrophy and early limitation of motion persist. Cardiac findings disappear and the electrocardiographic pattern reverts toward normal. The disease which had been a diagnostic problem is now obviously rheumatoid arthritis.

The usual laboratory guides of adult arthritis are valueless in Still's disease, for the antistreptolysin titer is high and the streptococcus agglutination titer is normal just as in rheumatic fever.⁶ Fortunately the differentiation is not imperative in the acute phase for the treatment indicated is the same.

The last type of patient is easily recognized because he is seen for the first time after the systemic reaction has subsided and he is left with only smoldering characteristic joint changes. There may be muscle atrophy, enlargement and limitation in motion of large joints, fusiform fingers with early flexion and extension contractures, limited motion in temporo-mandibular or cervical articulations. A shortened finger or two may be seen, the patient may limp because of old hip or knee involvement or an affected limb may be smaller in circumference than its opposite member. Subcutaneous nodules are occasionally present. Roentgenograms are typical.

LABORATORY FINDINGS

Most patients with Still's disease have an anemia (hemoglobin 70 to 80 per cent), and there is a general tendency to slight leukocytosis which may be marked in acute cases. Extremely severe leukocytosis is associated with a poor prognosis. In two fatal cases from this clinic the leukocyte count was over 30,000 per cu mm of blood. The urine is normal except the occasional patient in whom amyloid nephrosis develops.

Electrocardiograms show evidence of no abnormality in most cases despite the common occurrence of tachycardia. Some patients develop T-wave changes and a long P-R interval suggestive of rheumatic carditis. In those patients in whom arthritis persists and other symptoms subside, the electrocardiogram usually reverts to a normal pattern.

The erythrocyte sedimentation rate is moderately or markedly increased (30 to 130 mm in one hour—Westergren method). As noted before, the streptococcus agglutination titer is rarely elevated, whereas in adult rheumatoids it is positive in from 50 to 66 per cent of the cases. The antistreptococcus hemolysin titer is significantly elevated in Still's disease (mean of 250).

Joint fluid obtained by aspiration is no different from that obtained in adults.¹¹

DIFFERENTIAL DIAGNOSIS

The major difficulty is the differentiation of juvenile rheumatoid arthritis from rheumatic fever. The lack of response to salicylates is helpful in ruling out rheumatic fever and severe cardiac damage is

uncommon in Still's disease. Persistent joint symptoms with subsiding reaction in other systems usually indicate the diagnosis which may be possible to determine only with the passage of time. The antistreptolysin and streptococcus agglutination tests are of no value because results are similar in these two conditions. Still's disease and rheumatic fever are in many ways so similar that some observers suggest the name of rheumatoid or rheumatic state to encompass them both.

Tuberculosis occurs in older individuals and is usually mono-articular.

Haverhill fever may simulate arthritis of acute onset but the presence of a rash, the lack of chronicity and presence of a demonstrable causative organism distinguish it.

Brucellosis is less common in young children but must be considered when the diagnosis is in doubt. The agglutination or skin tests should be diagnostic.

PROGNOSIS

Two patients of the fifty six in our experience died. Death results from some complication as a rule. The most directly associated condition is perhaps amyloidosis.

Morbidity is definitely less in children than in adults. Children do well as a rule if proper supportive care is given; most are left with minor deformities when the process has burned itself out, while a very few have progression of changes until they are hopelessly crippled and confined to bed or wheelchair.

Recurrences after a maximum period of activity are not often seen in children but we occasionally see a patient who has repeated bouts of renewed activity extending well into adult life.

TREATMENT

There is no specific treatment for Still's disease and until we arrive at a clearer concept of the etiologic factor such a treatment may remain undiscovered. The same measures tried in adult rheumatoids have been tried in the juvenile patients, including vaccines, vitamins, cod liver oil, bee venom, foreign protein, artificial fever, induced jaundice, chrysotherapy, etc.

Because the process tends to be self limited, some nonspecific measures are important. Rest is necessary during the acute phase with high fever, leukocytosis, suggestion of myocardial damage. A child in this stage should be handled like one with rheumatic fever. Later as improvement occurs, restriction is governed by the temperature, erythrocyte sedimentation rate and the patient's sense of well being. On return to school, any excess activity such as gymnasium classes should be eliminated. In the transition period when school attendance is not practical, it is desirable to employ a home teacher.

A high-vitamin, high-caloric diet is essential. Added cod liver oil is of value if tolerated

Physiotherapy is used when the acute process subsides Gentle massage, dry or moist heat, and baths help depress muscle spasm and pain

Lightweight, posterior, molded plaster splints are made to prevent contractures and subsequent deformity of the knees, hips, elbows, wrists and fingers Splints are worn all night and part of the day If neck pain develops or flexion begins, a light plaster collar is used or in extreme cases head traction may be tried

Deformities already present must be corrected with skin traction, wedge casts or skeletal traction so that proper splints may then be applied ¹² If skeletal changes such as ankylosis or cervical fusion have occurred, the only measure left is operative interference to correct the deformity or improve posture

If anemia exists, repeated small transfusions and maintenance doses of iron are given Barbiturates are valuable for restless, sleepless patients particularly when given with salicylates

Salicylate given as the enteric-coated sodium salt often relieves pain more than any other one measure In children we prescribe 0.6 gm or more three or four times daily as needed The enteric coating causes fewer gastric upsets Simultaneous sodium bicarbonate is not given as it has been shown to reduce the level of salicylate in the blood ¹³

Our results with gold treatment have not been promising in children but we feel that this therapy merits a trial in patients not benefited by the usual supportive measures In this clinic we have used a preparation of sodium aurothioglucose (Solganol B Oleosum, Schering Corporation) The initial dose is 3 to 5 mg, increased to 25 mg but we no longer give larger doses even though children's tolerance is better than adults' The usual checks for toxicity must be employed and 600 mg constitutes an average course Some very young patients have received not more than 200 to 300 mg in a course A rest period of six weeks or more is given before gold is again instituted If there is no benefit from three courses of 600 to 800 mg each, the therapy is pursued no further It goes without saying that a knowledge of possible toxic effects and careful clinical and laboratory control of the patient is essential if chrysotherapy is instituted We have seen only two cases of moderately severe toxicity, both of which rapidly cleared on withdrawal of the drug There have been no fatalities with chrysotherapy

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MENOPAUSAL ARTHRITIS

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HERBERT S KUPPERMAN, Ph D , M D †

It is with some misgivings that the endocrinologist attempts to justify his intrusion, however limited, into the field of arthritis. Nevertheless, a symposium on this subject would not be complete unless the case for or against the hormonal role in so-called arthralgia and arthritis of the menopause is presented. At the outset it must be stated that if such a relationship does exist, it is neither generally recognized nor appreciated. Recently a whole issue of a journal was devoted to the study of the menopause.¹ In some dozen articles in this issue reference to the subject in question was made but once.²

Earlier in this century, the presumptive diagnosis of menopausal arthritis was frequently entertained but could not be substantiated. Some causal relationship between certain arthritic disorders and hormonal disturbances often had been suspected. For instance, in 1932 Leriche³ reported the case-findings of a patient who had been treated unsuccessfully for articular tuberculosis of the knee. The history suggested an hormonal basis for the affection since pain in the right knee accompanied her irregular bouts of menstruation. Complete recovery occurred subsequent to a course of estrogenic therapy. Leriche felt that the chronic articular affection in this particular instance was of ovarian origin and suggested the following explanation in such cases:

Any agency or agencies producing localized vasomotor equilibrium of hyperemic type may terminate in epiphyseal osteoporosis and the articular signs showing its presence consist of pain, limitation of movement, synovial swelling and other signs.

The advent of potent estrogenic preparations has yielded *ad hoc propter hoc* evidence which may permit the assumption that certain arthralgias and articular disorders have an endocrinologic background. Furthermore, room for further thought about this problem recently was provided by Selye.⁴

Despite the divergence of opinion as to the true nature of the arthritic pathology present at the menopause, the recognition of painful joints as a complaint of note associated with the climacteric should be more widely accepted.^{5 6 7} The controversial issue does not revolve

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around the recognition of the disturbance as an entity in the complex syndrome of the menopause but is concerned with the pathological classification of the arthritic condition. In addition, the manifold endocrine disturbance at the menopause has not aided in determining the etiological agent responsible for the initial episodes of arthralgia or exacerbations of the arthritis already present. This, too, has added to the lack of unanimity of the conceptions applied to the therapeutic approach to the problem.

With respect to the pathological picture seen at the menopause, it has been suggested⁸ that the condition may comprise one or a combination of the following:

1. *Arthralgia or arthrosis* A condition devoid of overt pathological manifestations but considered merely as a dysfunction expressed subjectively in terms of tenderness, painful motion and myalgia.

2. *Atrophic or rheumatoid arthritis* A condition associated with typical pathological changes and which, in many instances, is markedly aggravated by the climacteric.

3. *Hypertrophic or degenerative arthritis* A condition exhibiting the usual pathological picture of osteoarthritis which is either initiated or aggravated during the transitional period of the menopause.⁹

4. *Villous or climacteric arthritis* A form of arthritis which invariably involves the weight bearing joints, particularly the knees. While this has not been accepted as a definite entity, the claim is that it is neither an expression of atrophic nor hypertrophic arthritis.⁹ This latter affliction has been designated as gonalgia by Bohler and others.¹⁰

The manifestations of the menopause are characterized by a generalized hormonal imbalance. Decreased muscle tonus, tendency toward osteoporosis, disturbance of fluid balance, and inclination toward obesity are associated with the manifold physio-neuro-vascular disturbances of this period. The contradictory views negating the acceptance of menopausal arthritis as an entity have been dependent upon the complex pathology of the arthritides associated with this age period. The evidence associating the menopause with joint disability implicates the endocrine changes of the climacteric as one of the principal mechanisms responsible for precipitating the arthritic attack. In essence, it may be said that although the direct relationship of the glands of internal secretion to the production or alleviation of arthritis is not absolute, both the experimental and clinical evidence have adequately demonstrated that the endocrines play an important role in some types of joint pathology. Hormones, by their excess or lack, may act either as the etiologic or predisposing agent. It must be recalled that hormones are not merely chemical messengers, but also important metabolic catalysts.

The literature on the implication of the various endocrine glands, either in hypersecretory or hyposecretory states, is quite extensive and only a brief résumé pertinent to this discussion is here included. Selye

and his associates⁴ recently demonstrated the role of the adrenal glands in the production of arthritis through the experimental induction of rheumatoid arthritis in rats by the parenteral administration of massive doses of desoxycorticosterone acetate. Joint lesions were more readily produced with this adrenal cortical steroid in adrenalectomized or thyroidectomized rats when the animals were exposed to cold. In contrast, arthritis has been reported in deficiency states of the adrenal glands, as in Addison's disease.⁴ Similarly, the osseous changes observed in hypothyroid states, as in myxedema, have been found to predispose the patient to arthritic pathology.¹¹ Hyperthyroidism, on the other hand, often is complicated by some joint malfunction simulating rheumatoid arthritis.^{12, 13, 14} Dysfunction of the hypophysis has also been indicted as a cause of arthritis. In the menopause, the arthritic state has been noted in a large percentage of women going through this transitional period of life—a period of life fraught with numerous complaints of a physio-neuro-vascular character.^{15, 16} Probable contributory factors to the arthralgia of the menopause, in addition to the endocrine alterations, are increase in weight, vasomotor changes, emotional instability and hypertension.

Presumptive evidence of the relationship of the alterations in ovarian secretions to the inception of arthritic changes is based on the following observations:

- 1 Arthritis or arthralgia has been noted in 27 per cent of 1000 menopausal cases.¹⁷

- 2 The data on the sex incidence of adults between the ages of 37 and 54 exhibiting arthritic complaints show that five times as many females as males are affected with joint dysfunctions.¹⁵

- 3 Artificial menopause, induced by either x-ray irradiation or surgical extirpation of the ovaries, is frequently followed by complaints of an arthralgic nature.

- 4 Favorable response of such patients to estrogenic therapy.

- 5 Favorable effect of pregnancy upon rheumatoid arthritis.¹⁸

- 6 The arthritic process is usually limited to the period of transition during the menopause. Consequently, the process is usually not progressive and usually subsides after a few years without exhibiting residual changes.

- 7 Exacerbation of arthritic episodes during the menstrual period at the time of the menstrual cycle when estrogens are at a low level.

Other factors which are frequently present during the menopause and which deserve consideration are thyroid hypofunction and general increase in weight. The latter two factors must be strongly considered since their neglect in the treatment of menopausal arthritis may be responsible for failure in attaining a successful therapeutic climax to the problem at hand.

There is a great variation in the joints that are involved. Most frequently affected are the hands and weight bearing joints, such as the

less, hip joints, and ankles, less frequently are the shoulder joints, wrists, fingers, cervical and lumbar spines. The pathology in these painful joints may be negligible. The pathology may be limited to demonstrable changes in the joint activities or periarthritic involvement of the soft tissues resulting either in a fibrosis, myositis or bursitis.

THERAPY

The diagnosis of menopausal arthritis or arthralgia may be made principally from the history and the response of the patient to therapy. The therapeutic approach to the problem revolves around the attempt to correct satisfactorily the constitutional disturbances present at or during the menopause.

active principles of the thyroid hormone is noted and an exacerbation of the hyperthyroidism may result. To avoid an untoward response of the patient to thyroid therapy it is advisable to place the patient on small doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain of thyroid daily and, in the event that no evidence of intolerance is observed, the dose may be gradually increased until the desired clinical response is approached.

The rationale for thyroid medication is based on the following observations:

1. Thyroid therapy tends to correct certain physiological upsets at the time of the menopause and promotes an attempt to equalize the processes of catabolism and anabolism. The anabolic phenomena noted at the menopause are thus, in a measure, counteracted.

2. Estrogenic therapy may have an inhibitory effect upon the metabolic principle of the thyroid gland either indirectly by inhibiting the thyrotrophic hormone of the hypophysis or directly by inhibiting the metabolic hormone itself.^{23, 24, 25} Replacement therapy with thyroid, while not preventing this inhibition, will counteract the physiological depression of the thyroid gland.

Hall and Monroe¹³ noted that thyroid medication in patients with hypertrophic arthritis proved of value. Many of the patients with hypertrophic arthritis showed evidence of hypothyroidism and these investigators ascribed the beneficial effects following thyroid medication to better and increased joint nutrition.

General Supportive Methods—To increase the effectiveness of the endocrine regimen it is desirable, at times, to incorporate some orthopedic supportive methods, particularly when pain in the weight-bearing joints and postural joints strain are present. Notwithstanding the pain associated with movement of the affected joint, it is essential that there should be no limitation of motion of the joints. Perhaps complete *bed rest* should be resorted to only when motion is associated with excruciating pain. *Diathermic and heat treatments* are of value in increasing vasodilatation. *Orthopedic measures* may be needed. Such procedures, however, should only be incorporated into the therapeutic regimen under the direction of or by the specialist in this field. Of prime importance in the therapeutic approach to the menopausal arthritides is prevention of excessive increase in body weight. *Dietary control*, description of which is beyond the scope of this paper, may be said to depend upon a decrease of carbohydrate and fat intake.

It has also been suggested that *autohemotherapy* be used as a supplementary means in those patients in whom the pathologic condition has reached an advanced degree or in whom failure of response to estrogen therapy has been observed.²⁰ This latter therapy, in conjunction with artificial fever therapy, has been used with a fair degree of success in those patients in whom estrogen therapy has failed.

Another phase in therapy has been suggested by the interesting observations of Hench, that *jaundice*, infectious or toxic in origin, has an

ameliorating effect on atrophic and hypertrophic arthritis²⁷ Since jaundice, pregnancy and vitamin D in certain cases have been shown to have a beneficial effect on atrophic arthritis, it was suggested that a common denominator may be designated as the antirheumatic factor Since estrogens cholesterol (both found in increased amounts in the blood during pregnancy), vitamin D and bile salts all contain the phenanthrene nucleus Hench postulated that the antirheumatic principle of the future which would be effective in alleviating all types of arthritis would contain this chemical nucleus²⁸ On the other hand, another interpretation allying jaundice to the beneficial effect observed with estrogens in arthritis may be presented Undoubtedly when jaundice supervenes there is some interference with liver function and decrease in detoxifying activity of the liver Jaundice might well be associated with an increased amount of available estrogens in the blood stream and tissue since the gonadal hormones are metabolized by the liver,^{29 30 31} and impairment of liver function is associated with inadequate inactivation of estrogenic substances Thus jaundice attains physiologically what is observed after exogenous administration of estrogenic substances

The status of endocrinotherapy in the arthritides occurring at or after the menopause is not as yet defined³² There is much to be explored and a field for further investigation lies ahead The roles of infectious processes, faulty diet and elimination emotional stress and strain, vascular phenomena and fatigue are factors that cannot be ignored The purpose of this paper is to emphasize that the arthritic state associated with menopausal symptoms should not be underestimated or minimized that the internist gynecologist, orthopedist and the general practitioner take cognizance of the fact that judicious glandular therapy may afford relief when other measures have failed

SUMMARY AND CONCLUSIONS

1 Some hormonal dysfunction may be responsible for the inception or the exacerbation of many of the arthritides occurring at or after the menopause

2 The symptoms of menopausal arthralgia and arthritis may be ameliorated by estrogenic therapy A therapeutic trial employing large doses such as 2000 to 10,000 R U of estradiol benzoate or its equivalent every seven to ten days for a period of several months, is advisable Adjunctive thyroid therapy should be used in specific instances

3 Patients with arthralgia associated with the symptoms of change in life may show no demonstrable pathologic changes in the joints In those who do show changes atrophic arthritis is more common than the hypertrophic variety

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PNEUMOCOCCIC ARTHRITIS TREATED WITH PENICILLIN

Report of Six Cases

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IN only a few types of rheumatic disorders has penicillin achieved good therapeutic results. It is of no value in rheumatic fever,¹ rheumatoid arthritis,² osteoarthritis or gout. In the arthritides caused by organisms sensitive to penicillin such as pneumococci, streptococci and gonococci on the other hand, it has been used with moderate success.

Pneumococcic arthritis is rare. Bulkley³ found only 172 cases recorded from 1888 to 1914. In this group, the arthritis was associated with pneumonia in about 70 per cent of the cases. Of the remaining 30 per cent, less than half had an extrapulmonary pneumococcic focus and the rest had no discoverable source of the infection. Of 31,757 cases of pneumonia reported by various authors, pneumococcic arthritis occurred in ninety-seven,⁴ an incidence of one in 327.

Until the advent of chemotherapy, the treatment for this condition frequently included surgical procedures. For example, arthrotomy was performed in ninety-one of the cases in Bulkley's series. In 1944, however, Blankenhorn and Grupen⁵ reported eleven cases of pneumococcic arthritis, all treated with repeated aspirations and sulfonamide or specific serum. Of these the only case that required incision and drainage was seen before the sulfonamides were in use.

The present report is based on six cases of arthritis due to type-specific pneumococci, observed on the Third (New York University) Medical Division of Bellevue Hospital. In four of the cases the arthritis occurred during the course of a pneumonia with bacteremia. These have been partly dealt with in a recent paper by Tillett, McCormack and Cambier.⁶ In the fifth case, the arthritis was associated with pneumococcic endocarditis. In the sixth, there was no pneumonia, bacteremia or other source of the organism. Five of the six patients were seen in 1943 and 1944 and were treated with penicillin, three intra-articularly as well as systemically. One patient was observed in January 1937 before effective chemotherapy for pneumococcic infections was known and in this case specific antiserum was used.

CASE REPORTS

CASE I—J S, a white man aged 48, was admitted with pneumonia of the right lower lobe of four days' duration. Arthritis of the right knee had developed on

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the third day of his illness. The joint was painful, swollen, tender, warm but not red. Twenty five cubic centimeters of thick green purulent fluid were aspirated in which by direct smear many gram positive diplococci were demonstrable. No other joints were inflamed. Type I pneumococcus was recovered from the blood.

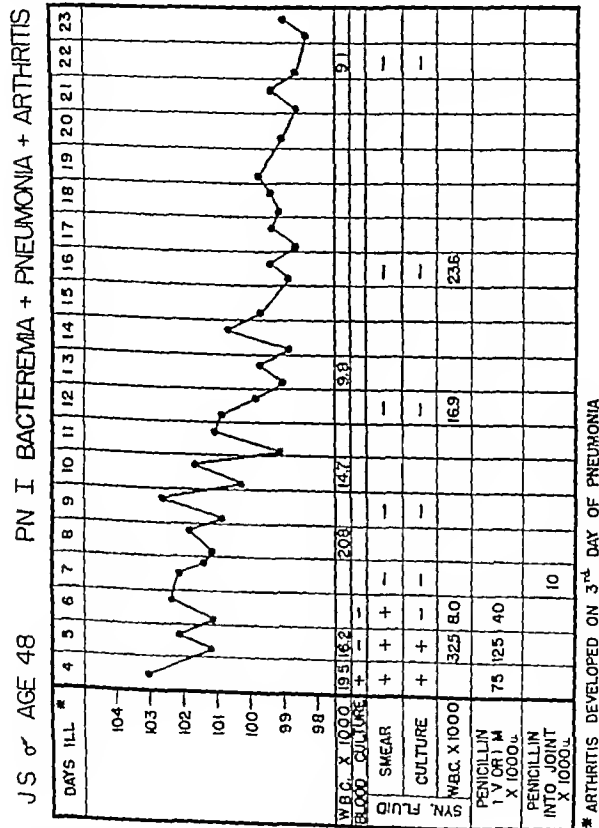


Fig 86 (Case I) —Clinical course

culture and from the knee fluid. Seventy five thousand units of penicillin were administered parenterally. The next day the blood culture was sterile, but cocci were still shown to be present in the synovial fluid on . . . One hundred twenty five thousand units of penicillin were . . . and intravenously on the second day. On the third day the . . .

fluid was sterile although a smear showed an organism with a "moth-eaten" appearance. Forty thousand units of penicillin were given intramuscularly that day. On the fourth day, 10,000 units of penicillin were introduced into the joint.^{*} The culture and smears of the fluid obtained that day and on four subsequent taps were free of bacteria. After each tap, fluid reaccumulated but in gradually diminishing quantities. It became lighter in color and thinner in consistency although



Fig 87 (Case I) —X-rays of both knees showing no changes in the articular structures

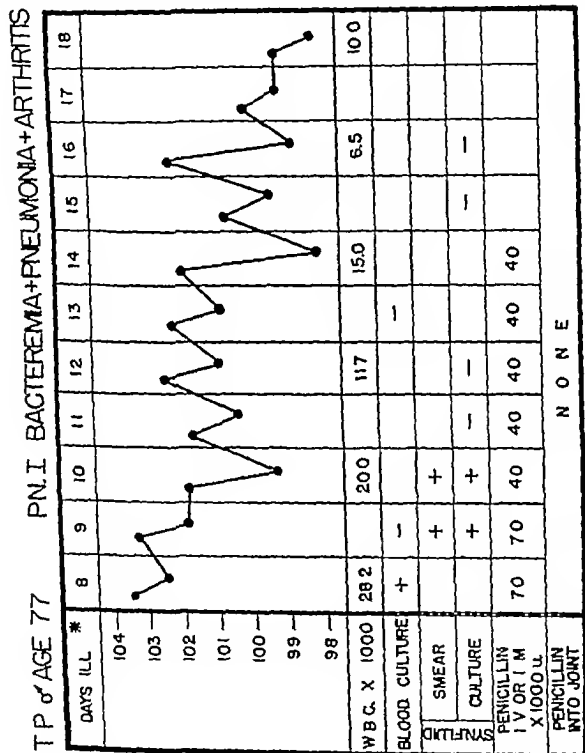
it continued to show pleocytosis. Repeated x-rays of this joint showed evidence of effusion but no abnormal changes in the bone. The temperature gradually declined and reached a normal level on the thirteenth hospital day. The patient was discharged on the thirty-ninth hospital day. He was able to bear weight and walk with the aid of a cane. The knee was somewhat stiff but not painful, tender or warm and showed no signs of fluid (Figs 86 and 87).

Summary —After the administration of penicillin intravenously, intramuscularly and intra-articularly, the blood and synovial fluid of a patient with Type I pneumonia and monarticular arthritis became sterile and good joint function followed.

CASE II —T. P., a white male aged 77, entered the hospital with lobar pneumonia of the right upper and middle lobes on the eighth day of illness. He received no chemotherapy before then. One day prior to admission, the right knee became swollen, painful, tender and warm but not red. No other joints were involved. A blood culture taken on admission yielded Type I pneumococcus. The white blood count was 28,200 and the temperature 103.4° F. Seventy thousand units of penicillin were given intravenously and intramuscularly. The next day the blood culture was sterile. Eighty-eight cubic centimeters of thick, green, puru-

^{*} For intra-articular use, 10,000 units of the sodium salt of penicillin were included in 1 cc of saline.

lent fluid were removed from the knee. Gram positive diplococci were seen on direct smear and Type I pneumococcus grew out on culture. Active penicillin was demonstrated in vitro to be present in this fluid. Seventy thousand units of penicillin were again given parenterally. On the third day 40 cc. of thick light brown fluid were removed from the joint and this time also the smear and culture were positive. Forty thousand units of penicillin were given intramuscularly that day.



* ARTHRITIS DEVELOPED ON 7th DAY OF PNEUMONIA
Fig 88 (Case II) - Clinical course.

On the fourth day a third tap yielded 45 cc. of yellowish brown fluid which proved to be sterile on culture. Fluid reaccumulated after each tap although both it and the blood remained sterile. The temperature reached a normal level on the eleventh hospital day. In all 840,000 units of penicillin were given parenterally, none of which were introduced directly into the joint. Osteoarthritic changes were seen on x-ray but there was no destruction of bone. Because of a flexion deformity which developed, traction was applied and later a wedged plaster cast was made.

The knee showed little further improvement and the patient was transferred to the orthopedic service. Six months later he developed acute toxic hepatitis with fever, leukocytosis, jaundice and hepatomegaly and died on the fourth day of this illness (Fig 88)

Summary—An aged patient with osteoarthritis, a Type I bacteremic pneumonia and monarticular arthritis was treated with penicillin parenterally. The blood stream became sterile in twenty-four hours, the synovial fluid not until ninety-six hours had elapsed. A flexion deformity developed and prolonged orthopedic care was necessary.

CASE III—G R, a 76 year old white woman, entered the hospital with pneumonia of the left lower lobe on the fourteenth day of illness. Type VIII pneumococcus was obtained on blood culture. Since the age of 40 she had had pain, stiffness and deformity of both wrists, elbows, knees and ankles. On the seventh day of her pneumonia both wrists and hands became markedly swollen, painful, tender, red and more limited in motion than before the present illness. There were no acute changes in the other joints. In x-rays of the hands excessive production of bone at the distal interphalangeal joints was noted, typical of osteoarthritis, and at the wrists, marked narrowing of the joint spaces with some destruction of bone at the articular surfaces, consistent with a diagnosis of rheumatoid arthritis (Figs 89 and 90). Thick, brown, purulent fluid removed from the left wrist on the second hospital day showed gram-positive diplococci on smear and Type VIII pneumococcus on culture.

Seventy thousand units of penicillin were given intravenously and intramuscularly. On the following day the blood culture was sterile. On the fifth day after 270,000 units of penicillin had been given parenterally, 3 cc of purulent material was removed from the left wrist and 10,000 units of penicillin were instilled. A smear of this fluid showed a few gram-positive diplococci but the culture was sterile. Forty thousand units of penicillin were given intramuscularly on each of the following three days. Clinically both wrists and hands showed marked improvement, and complete subsidence of the swelling and redness occurred though motion remained markedly limited. The patient left the hospital against advice on the twenty-eighth hospital day (Fig 91).

Summary—In a patient 76 years old who had had a long-standing and advanced rheumatoid arthritis, a suppurative polyarthritis occurred during the course of Type VIII pneumonia with bacteremia. After the administration of penicillin intravenously, intramuscularly and into one of the joints the blood and the synovial exudate became sterile and the joints returned to their former state. The joint into which no penicillin was injected did as well as the one that was treated locally.

CASE IV—M McK, a 65 year old white woman, was admitted with signs of pneumonia in right and left lower lobes. She was completely disoriented and could give no history. The heart showed auricular fibrillation at a rate of 160. Most of the joints had undergone osteoarthritic changes. The right knee was swollen, warm, tender but not red. The temperature was 104° F and the white blood count 8000. A Type XII pneumococcus was recovered from a blood culture taken on admission. A few cubic centimeters of purulent fluid were removed from the right knee and gram-positive diplococci were seen on smear and Type XII pneu-



Fig 89 (Case III) —X rays of both hands and wrists (lateral view) Marked soft tissue swelling is present at the wrists and metacarpophalangeal joints

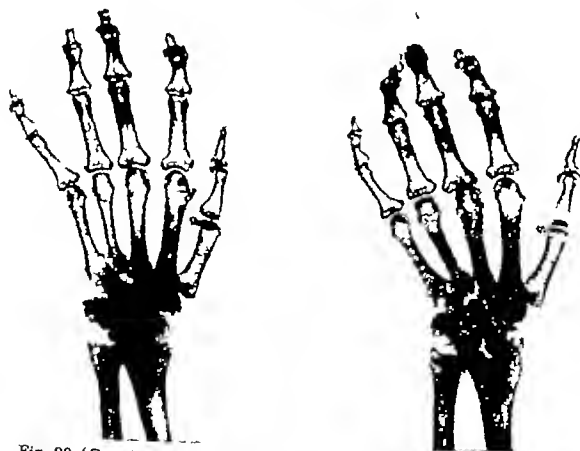
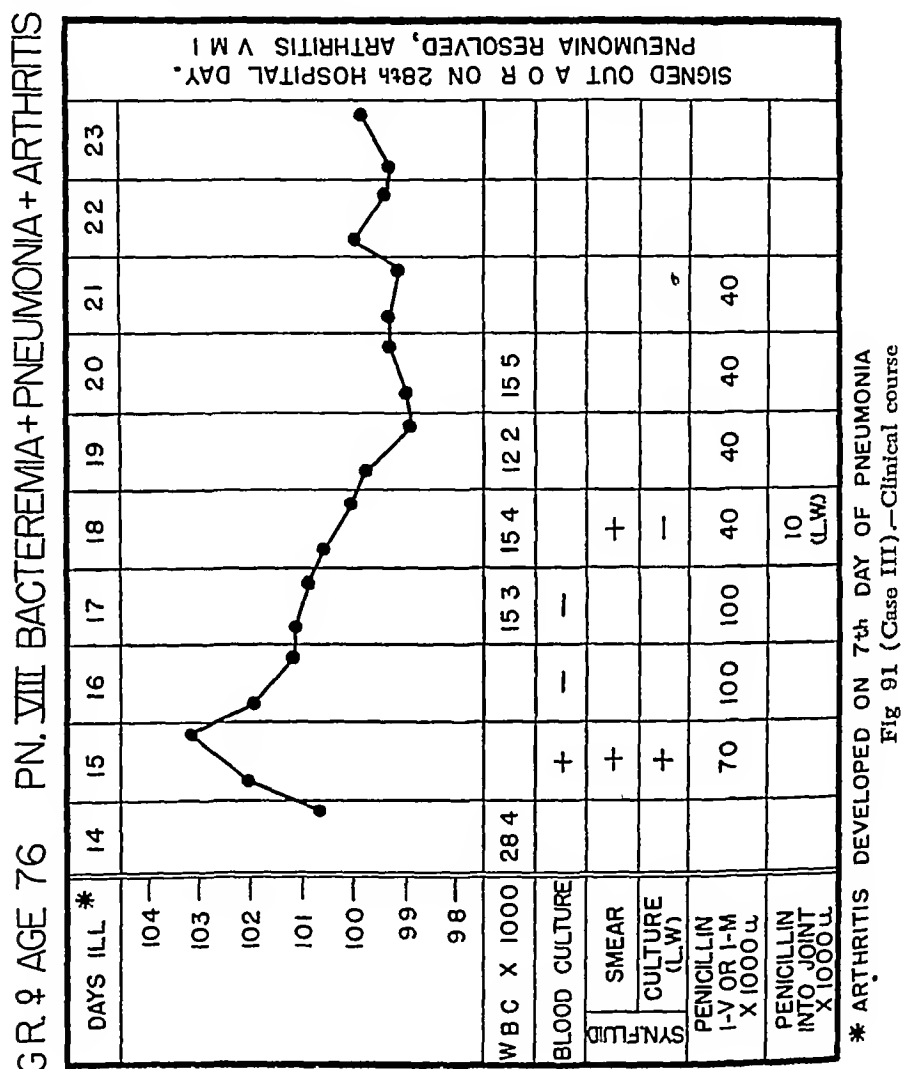


Fig 90 (Case III) —X rays of both hands and wrists (anteroposterior view) At the distal interphalangeal joints overproduction of bone narrowing of joint spaces and widening and irregularity of the joint surfaces are present. At the wrist joints destruction of bone, narrowing of joint spaces and localized areas of osteoporosis are seen

cococcus was recovered on culture. One hundred forty-five thousand units of penicillin were given intramuscularly and intravenously within the first two days. The bacteremia cleared after 70,000 units were administered. The patient died fifty-eight hours after admission.



Summary—In a moribund patient with rapid auricular fibrillation and Type XII bacteremic pneumonia with monarticular arthritis of unknown duration, the administration of penicillin was followed by clearing of the blood stream but death occurred on the third day.

CASE V—M L, a Negro woman of 65, was admitted complaining of inability to walk because of severe pain, swelling and stiffness of both knees for the past six days. Since the age of 40 these joints had been stiff and painful from time to time. The patient was markedly obese, weighing over 300 pounds. Both knees were swollen, painful, tender, warm, stiff but not red. X-rays of these joints

showed advanced osteoarthritic changes with marked effusion in the suprapatellar spaces. The temperature on admission was 103.4 F and the white blood count 12,900. The blood culture was sterile. The Wassermann and Kahn reactions were

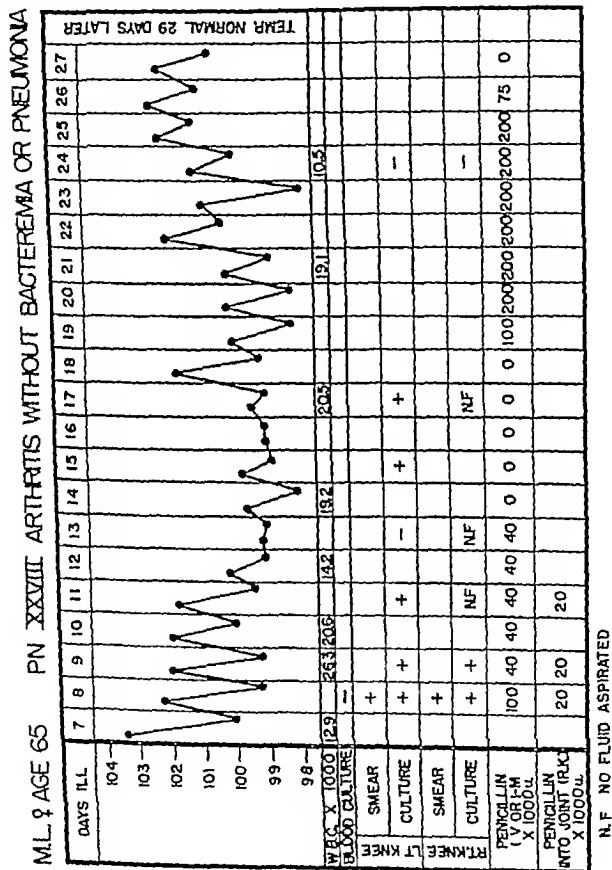


Fig 92 (Case V) - Clinical course.

positive for the blood but negative for the spinal fluid. Purulent fluid aspirated from each knee showed gram positive diplococci on smear and Type XXVIII pneumococcus on culture.

One hundred thousand units of penicillin were given parenterally and 20,000 units were introduced into the right knee. On the following day a culture of the fluid from each knee was again positive, 40,000 units were given intramuscularly and 20,000 units into the right knee. On each of the next four days 40,000 units of penicillin were given intramuscularly. On the fourth day of therapy no fluid had been obtained on tapping the right knee but that cultured from the left was still positive for Type XXVIII pneumococcus. Twenty thousand units were again injected into the right knee. The next tap of the left knee on the seventh day resulted in a sterile fluid, no fluid could be aspirated from the right knee. On the ninth and eleventh days the exudate from the left knee contained pneumococci again. A more intensive course of penicillin therapy was then instituted, the drug being given intravenously and intramuscularly. On the sixth day of this second course the fluids removed from both knees were sterile on culture. The temperature, however, fluctuated between 101° F and 102.4° F. Both lower limbs became diffusely swollen and tender. It was thought that a bilateral thrombophlebitis and cellulitis had developed. Penicillin had been discontinued and a six day course of sulfadiazine was administered without definite improvement. During the next four weeks the temperature slowly receded. The edema of both limbs disappeared and the swelling of both knees diminished. With the aid of physical therapy and general care the patient was finally able to get about on crutches. She was discharged 202 days after her admission (Fig 92).

Summary—An elderly syphilitic Negress, who developed a Type XXVIII pneumococcus arthritis in both knees, which had previously been the seat of a long-standing osteoarthritis, was treated with penicillin parenterally including direct injection into one joint. The exudates of both joints eventually became bacteria-free but clinical improvement was slow and was retarded by diffuse cellulitis of both lower limbs.

CASE VI—F LaS, a white woman of 47, entered the hospital because of congestive heart failure. She had been admitted twice in the past six months for the same reason. The diagnoses previously reached were essential hypertension, hypertensive and arteriosclerotic heart disease with dilatation of the aorta, sclerosis of the coronary arteries and myocardial fibrosis. She had been given digitalis and diuretics during the past year. On admission, the cause of a spiking temperature reaching 105.4° F was not apparent until the twenty-eighth hospital day when a blood culture yielded 100 colonies of Type V pneumococcus per cubic centimeter. This occurred on January 10, 1937, before an effective sulfonamide derivative for the pneumococcus was known. The patient was treated with Type V antiserum. On the second and third days of specific therapy, respective blood cultures yielded 150 and 200 colonies per cubic centimeter. Seven days after the bacteremia was demonstrated and on the fourth day of specific therapy, an effusion was noticed in the right knee joint. It was swollen, painful and tender. Twenty cubic centimeters of cloudy fluid were removed and found to contain Type V pneumococcus. Two days later showers of petechiae appeared in the conjunctivae and skin, and on the following day the patient died. A total of 1,092,000 units of antiserum had been given intravenously without effect. None was introduced into the joint. While there was no evidence of lobar pneumonia it is quite possible that the changes due to congestive failure obscured the signs of a bronchopneumonia. The cause of death was thought to be a pneumococcus endocarditis. An autopsy was not done (Fig 93).

Summary—Pneumococcus Type V bacterial endocarditis developed in a patient with arteriosclerotic and hypertensive heart disease and

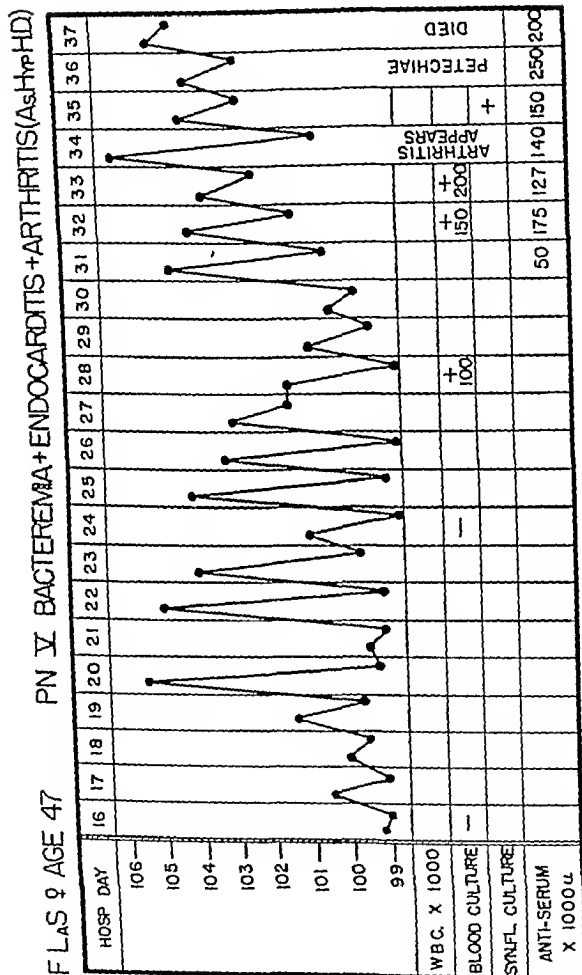


Fig 93 (Case VI).—Clinical course.

was followed by a purulent monarticular arthritis. Neither the bacteremia nor the arthritis responded to specific antiserum which was used in this case before the advent of chemotherapy.

COMMENT

Following penicillin therapy the blood and synovial fluid became sterile in every case. The blood became free of bacteria one or more days before the joint exudate. Whether it is necessary to inject penicillin directly into the joint besides giving it systemically cannot as yet be stated with finality. In each of the two cases with bilateral, symmetrical joint involvement penicillin was injected into one joint but not into the other, yet there was no significant difference either clinically or bacteriologically between the treated and untreated joints. Such results are understandable when it is recalled that penicillin crosses inflamed synovial lining in either direction, from blood to joint fluid or reversely. Rammelkamp and Keefer⁷ instilled 10,000 units of penicillin into an inflamed knee joint and recovered some of it in the serum twenty-five minutes later. The maximum blood level (0.019 units per cc) was reached in seventy minutes and penicillin was still present in the circulation four hours later. Herrell, Nichols and Heilman⁸ found that penicillin after intramuscular or intravenous administration could reach the synovial fluid of suppurative joints and in some instances attain a concentration approximately half that of the blood. Balboni, Shapiro and Kydd⁹ determined that after intramuscular administration, penicillin readily penetrates the joint fluid (rheumatoid arthritis) and that maximum antibacterial quantities persist longer in it than in the blood serum. Tillett⁶ demonstrated in two of the cases included in this series (Cases II and III) the presence of active penicillin that diffused from the blood stream into the articular exudate. On the other hand, these cases also show that direct injection of penicillin into an articular cavity does no detectable damage to the surrounding tissues, and the high concentration thus achieved may possibly stop more promptly the destructive processes in a purulent joint.

In most of the cases reported here, effusion recurred in the inflamed joints, necessitating repeated aspirations. This reaction occurred in the joints not injected as well as those injected with penicillin. Furthermore, fluid reaccumulated for a time, varying from days to weeks, after the exudate had been found free of bacteria on several successive taps.

In none of the cases in this series was a migrating polyarthritis observed. This clinical point is helpful in distinguishing this type of arthritis from gonococcic or rheumatic polyarthritis. Pneumococcic arthritis has an affinity for large joints, particularly the knees. In Bulkley's series, the knee was the joint most frequently attacked. In 75

6 CASES OF PNEUMOCOCCUS ARTHRITIS

6 CASES OF PNEUMOCOCCUS ARTHRITIS

NAME	AGE	TYPE	BACTEREMIA	PNEUMONIA	DAYS AFTER ONSET	OTHER FOCI	JOINTS AFFECTED	PRECEDING ARTHRO-PATHY	NO. OF TAPS	PENICILLIN			RESULTS	
										DAYS	I V OR I M	I A	SYN. FLUID	JOINT FUNCTION
J.S. ♂	48	I	Y	Y	3	N	L. K.	N	9	4	240,000	10,000	STERILE	V.M. IMP.
T.P. ♂	77	I	Y	Y	7	N	R. K.	OSTEO.	6	7	340,000	0	STERILE	IMP.
G.R. ♀	76	III	Y	Y	7	N	R. & L. W.	RTD + OSTEO.	2 (L)	7	430,000	10,000 L.W.	STERILE	V.M. IMP.
M.W.K. ♂	65	III	Y	Y	—	N	R. K.	ADV. OSTEO.	1	2	145,000	0	DIED 59 HRS. AFTER ADM. (BL. CULT. STERILE)	
M.L. ♀	45	III	N	N	—	N	R. & L. K.	ADV. OSTEO.	7	8+8	300,000 + 1,375,000	60,000 R. K.	STERILE R. & L.K.	V.M. IMP.
F.L.S. ♀	47	II	Y	?	—	EMDOC.	R. K.	N	1	1,092,000 UNITS ANTI-SERUM I V NO CHEMOTHERAPY (1937)			DIED (BACTEREMIA PERSISTED)	

Symbols

Y = Yes
N = NoL. K. = Left knee
R. K. = Right knee.

R. & L. W. = Right & left wrist.

Rtd = Rheumatoid.

I V = Intravenous

I M = Intramuscular

I A = Intra articular

V M Imp = Very much improved.

Fig 94—Summary

per cent of his cases only a single joint was involved. In five of the six cases here reported the affected joint was the knee and in four the arthritis was monoarticular

The pneumococcic infection was superimposed on a preexisting arthropathy in four of our cases. Rufus Cole¹⁰ drew attention to this predisposing factor in 1902 and several cases of gout as well as many of osteoarthritis and rheumatoid arthritis have been reported in which the involved joints were subsequently infected by the pneumococcus. Since penicillin has no favorable effect on these underlying joint diseases, one cannot anticipate more than a return to a former state of articular function from successful treatment of the superimposed bacterial infection.

As has been observed by others, the prognosis as to life in this disease is governed not by the articular changes but by the severity of the extra-articular infections such as bacteremia, pneumonia, endocarditis and meningitis. Two of our six patients died, one after an overwhelming septicemia and the other with an endocarditis. In neither instance did the arthritis significantly influence the outcome.

SUMMARY

Six cases of pneumococcic arthritis due to Types I, V, VIII, XII and XXVIII are reported. Penicillin was administered intravenously and intramuscularly in five cases, three of which also received it intra-articularly. Prompt sterilization of the blood stream and subsequent sterilization of the synovial fluid followed. Surgery was not necessary in any instance.

Prognosis as to life is governed not by the arthritis but by the severity of the associated extra-articular infection. Two patients died, one of bacterial endocarditis and the other in a moribund state fifty-eight hours after admission.

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THE RECOGNITION AND MANAGEMENT OF GOUT

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THERE is good historic evidence that gout was known to Hippocrates and that colchicum, which is still considered a specific remedy for it, was used in its treatment nearly 1500 years ago. Few diseases would seem to have got off to a better start—both as to diagnosis and as to treatment. Nevertheless, gout remains one of the most poorly diagnosed and treated of diseases. It is by no means an uncommon disease, and it is usually quite easy to diagnose if one is familiar with its clinical picture. Its treatment is quite satisfactory in the majority of cases.

THE CLINICAL PICTURE OF GOUT

The Acute Attack.—A fall in barometric pressure, excess physical exertion, an acute infection or a surgical operation, the administration of certain drugs such as gynergen, thiamine or liver extract and overindulgence in alcohol or food may precipitate an attack of gouty arthritis. Often no cause can be found for the attack. In all cases, however, the patient is basically a gouty person.

A spontaneous diuresis may precede an attack. Often the patient is awakened at night with severe joint pain. The affected joint is swollen, exceedingly tender and the skin for a considerable surrounding area is red, pink or violet-colored. The pain and tenderness seem out of proportion to the area involved, and are greater than with a non-gouty acute arthritis. As the attack subsides the affected area often desquamates. The fever may rise to 103° F at the height of the attack. In some cases there is irritability, depression and gastric upset. In the earlier stages of the disease there is complete disappearance of all signs and symptoms when the attack subsides so that no trace of joint damage remains.

Location of Gouty Arthritis.—The small and medium joints are most commonly affected. Early in the disease a single joint is involved, but as the disease progresses several joints, either together or in sequence, are affected in each attack. The first metatarsophalangeal joint (the "bunion" joint) is eventually involved in the majority of cases and is therefore a signal for us to suspect gout. On the other hand, in any given episode this joint is just as likely as not to be spared so that normality of the "bunion" joint in no way lessens the probability of gout being the cause of an acute arthritis.

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The Life History of Gout.—More than 95 per cent of cases of gout occur in males. A diagnosis of gout in the case of a female is acceptable only after the fullest verification. The first attack seldom occurs before the age of 35 although episodes dating from childhood have been reported. At first there are acute, sharply circumscribed episodes lasting three to ten days which disappear leaving no residual joint pain or damage. The second attack may occur a year or so later. Eventually the episodes are more severe, last longer and recur at shorter and shorter intervals and involve several joints at a time. After several years, remissions fail to be complete and a state of chronic gouty arthritis sets in. By this time tophi are nearly always present and the serum uric acid is almost always elevated.

Ultimately a state of quiescence is reached in which there is little pain and in which exacerbations are mild or hard to identify. Joint function is limited by large uratic deposits which may ulcerate and which should be surgically removed. At this time, complications such as renal failure and visceral tophi occur.

The Differential Diagnosis of Gout.—The above pattern of periodic acute arthritis with absolute freedom from pain and joint damage in the intervals sets gout apart from all other common varieties of arthritis and rheumatism. This fact, so ably emphasized by Hench,¹ may of itself be sufficient to make the diagnosis. The few minutes necessary to elicit it in taking a history are indeed well repaid. Naturally, this pattern is not yet established at the time of the first attack of gout, but in this case one may note the nocturnal onset, the location in the "bumion" joint, the severity of the pain, the bluish-red discoloration and subsequent desquamation. All these favor the diagnosis of gout rather than some other type of acute arthritis. The periodic pattern of gouty arthritis need seldom be confused with the recurrent bouts of rheumatic fever and has nothing whatever in common with the relentless downhill course of rheumatoid arthritis or the progressive disability of osteoarthritis.

Other types of periodic arthritis to be considered in the differential diagnosis are intermittent hydrarthrosis which is usually confined to the knees, arthritis intermittens which recurs regularly at certain phases of the menstrual cycle, and palindromic rheumatism as recently described by Hench² (Space does not permit an adequate discussion of these periodic syndromes.) Erythema nodosum occurring near a joint, such as the ankle or dorsum of the foot, and not accompanied by the characteristic pretibial lesions may very closely simulate the appearance of gout and may go on to desquamation. The moderate degree of pain and the fact that it is not greatly increased by joint motion, the good response to sulfones and/or penicillin and the normal serum uric acid distinguish this from gout. Occasionally this condition may recur annually.

Pathogenesis of Gout—Gout is associated with an inherent fault in purine metabolism which persists throughout life and which can not be eradicated although its clinical manifestations may be controlled. There is no agreement as to what the fault in purine metabolism is or as to how it causes the symptoms of gout, but the retention of uric acid as shown by elevated serum uric acid and uratic tophi is constantly found in the later stages of the disease. Purines are derived from cell nuclei and are broken down to uric acid and urates and excreted as such. They are not to be confused with urea.

Laboratory Findings in Gout.—1 *Elevation of Serum Uric Acid*—Normally serum uric acid averages 4 mg and is below 6 mg per 100 cc (Determinations on whole blood are less reliable and should be abandoned.) An elevation in serum uric acid occurs in a number of diseases such as polycythemia, renal failure and toxemia of pregnancy. Fortunately, joint lesions are not ordinarily a part of these diseases so that gout is seldom confused with them. Leukemia is a possible exception since both hyperuricemia and joint pain and swelling may coexist.

In general the serum uric acid level roughly parallels the severity of gout. However, there are many exceptions to this generalization. Certain apparently normal individuals, especially those of gouty ancestry, may have an elevated serum uric acid without clinical evidence of gout. On the other hand, the serum uric acid may be normal in a known case of gout—even during the acute attacks. From a practical point of view one may simply remember that when a serum uric acid well above the level of 6 mg. per 100 cc. is found in a person with joint symptoms, the diagnosis is gout till proved otherwise.

2. *Polymorphonuclear leukocytosis and rapid sedimentation rate* are often found in the acute attack. It is interesting that both these evidences of infection as well as fever should occur in a noninfectious disease of purely metabolic pathogenesis.

3. *Roentgenography*, particularly in late cases, may show multiple punched-out areas at the ends of the small bones of the hands and feet. These are individually indistinguishable from similar lesions found in rheumatoid arthritis. When multiple they favor gout as the diagnosis. Ordinarily they are suggestive rather than diagnostic of gout.

4. *Uratic Tophi*.—Material from tophi, if chemically identified as urates, makes the diagnosis of gout conclusive. Discharges of calcium phosphate and carbonate in cases of calcinosis ("calcium gout") are not easily confused with uratic tophi. Tophi occurring near the extensor aspect of the elbow should not be confused with rheumatic nodules of rheumatoid arthritis or rheumatic fever. Those in the ear may be mimicked by sebaceous cysts.

TREATMENT OF THE ACUTE ATTACK

On the whole, the treatment of gout is quite satisfactory. It differs radically from the treatment of other forms of rheumatism so that it is exceedingly important to make a correct diagnosis.

Treatment of an attack of gouty arthritis should begin with the very first warning of its approach. If the attack is well established it is that much more difficult to break it up. A strong saline cathartic followed by bed rest and protection of the affected joint comes first. Local applications of either heat or cold may give some comfort but codeine or morphine may be necessary. Colchicine has a specific action in relieving the pain and should be given in doses of $\frac{1}{100}$ gram every three hours. It may be continued through the night if the pain is severe. It is very important to discontinue it when diarrhea, nausea or vomiting occurs since these are the warnings of intoxication. A profuse diarrhea with acute nephritis and an ascending paralysis ending in respiratory failure and death have been reported from as little as 6 mg. of colchicine ($\frac{1}{10}$ gram) or 15 cc. of the tincture. The average patient tolerates one to three days of treatment before diarrhea begins. Colchicine will not relieve the pain of other types of acute arthritis. It also seems to have an action in shortening the gouty attack.

From the beginning of the attack one should also give 15 to 20 grains of salicylates four times a day, with double the amount of sodium bicarbonate and 2000 to 2500 cc. of fluids. This should be continued until the serum uric acid returns to normal and stays there. A purine-free diet completes the ordinary management of the acute episodes.

On this program most cases are relieved of symptoms in a few hours or a few days. I cite one case of a man who had been bedridden for three months with constant pain who was free of pain and walking after three days of the above program. Naturally, many responses are not so gratifying. In no case must it be forgotten that the patient still has gout and that he will suffer increasingly severe and crippling attacks unless an interval program of gout control is set up and rigidly followed.

THE INTERVAL MANAGEMENT OF GOUT

A gout-control program consists essentially of psychotherapy, diet and drugs and has been proved to reduce greatly the number and severity of attacks. It is entirely reasonable to suppose, without proof, that it also delays and perhaps prevents the late complications and disabilities of the gouty state.

Psychotherapy.—The patient should be convinced of the correctness of his diagnosis and should understand that he has an inborn and unalterable inability to deal with uric acid-making foods. He

should be taught how to avoid the precipitating factors of the acute attacks and the importance of early institution of correct treatment. It has not infrequently been my experience to find that a diagnosis of gout has previously been made—perhaps ten or fifteen years ago—and that, since the patient neither believed nor understood it, he has gone from doctor to doctor seeking a "cure." Such patients may have been subjected to violent and (for gout) useless treatments, such as removal of questionable teeth and tonsils, protein shock, or even gold therapy. All such risks and misfortunes could have been avoided and the course of the disease probably retarded if the patient had had a correct understanding of his illness.

Diet.—Since uric acid is derived from cell nuclei, the basic principle of a diet for gout must be the avoidance of those foods in which nuclei are abundant. This automatically eliminates all meats, fowl and fish and especially meat extractives and gravies. The resulting protein deficit is made up by eggs, cheese, nuts, peanut butter and partly refined cereals all of which contain only traces of purines. Excess intake of fat, and all alcohol must be avoided since both may precipitate an attack. The patient may also note that certain foods are especially apt to offend and his observations should be welcomed. Tea and coffee are permitted. For full information as to the diet, standard texts should be consulted and an illustrative diet sheet given the patient. Although dietary restriction should be life-long, the degree of restriction may be lightened if the clinical condition of the patient and his serum uric acid level permits. In favorable cases certain meats may be permitted once or twice a week. The many patients who obtain relief from a low purine intake are more than willing to adhere to this rather gloomy menu.

Drugs.—When the serum uric acid level cannot be lowered by diet alone, salicylates, alkalies and forced fluids as recommended above for the acute attacks may be instituted for three or more days per week as a permanent program. Daily doses of $\frac{1}{120}$ grain of colchicine may be added to this program without harm and perhaps with benefit. Also to be considered is the addition of 150 grains (10 gm.) of glycine daily as recommended by Quick.²

Cinchophen should be considered if the above plan is not effective. The patient should be acquainted with the occasional (less than 1 per cent) incidence of fatal acute yellow atrophy of the liver which may follow its use. The accepted mode of administration is 0.5 gm thrice daily for three consecutive days per week as governed by the serum uric acid level and clinical response. Abundant fluid, carbohydrates and alkalies should be taken as a preventive against liver damage and uratic kidney stone. It may be that methionine will protect the liver to some extent although this has not yet been proved. The patient and his physician should both watch for scleral icterus.

and pruritus as early signs of intoxication. The drug should immediately and permanently be withdrawn if these signs appear.

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ROENTGEN THERAPY FOR RHEUMATIC DISEASES

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EXCEPT for recently developed methods of chemotherapy for most of the acute bacterial infections affecting joints—different varieties of specific infectious arthritis—the treatment for rheumatic diseases has not evolved into a routine procedure that has met with complete or even general agreement among those responsible for the management of this group of illnesses. The chief reason for this lies in the fact that the etiology for common forms of rheumatism has not been learned, consequently various treatment procedures are instituted depending upon either the different concepts of this disease of unknown etiology or upon the results of trial of various forms of therapy which arise entirely upon an empirical basis. In the latter category belongs roentgen therapy.

Soon after the discovery of x rays, their effects upon different forms of rheumatic disease were discussed by Sokolow,¹ Stenbeck,² and Anders Daland and Pfahler.³ The generally favorable reports of Kohler,⁴ Kreuzwald,⁵ Kraus,⁶ Kahlmeter,⁷ von Pannewitz,⁸ Langer,⁹ Scott¹⁰ and Garland¹¹ have stimulated a wider interest in exploring this form of treatment for rheumatism. The author and his collaborators began their studies in 1938 and reported^{12, 13} certain observations in 1941.

CASE REPORTS

This clinic is planned to present representative cases which will lead to discussion of practical considerations of roentgen therapy for rheumatic diseases.

Case I. Early Spondylitis Rhizomélisque Treated by Roentgen Therapy with Excellent Results

R. S. an unmarried white man, aged 21 was admitted to the hospital with the chief complaint of pain in the low back and legs. This illness began fourteen months previously with intermittent aching pain in the thighs and buttocks bilaterally. No recognized infection or trauma had preceded or accompanied the onset of these rheumatic pains. The frequency and severity of the pain increased but he continued his occupation of farming. Ten months before admission he began to notice pain in the low back chiefly in the region of the sacroiliac joints. The back pain was of an aching character which soon became constant, it was aggravated by jarring, stooping, lifting, turning and rising from bed. The pain gradually spread so that at the time of admission it involved the entire sacral lumbar

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and lower two thirds of the dorsal back. The leg pains gradually lessened but stiffness of the back became increasingly bothersome. For eight months he had noticed that sneezing and coughing caused sharp pain in the entire back and at times radicular pain in the thoracic region. Chest expansion reduced in depth and breathing was at times difficult. Strength and ambition decreased progressively, and ease of fatigue was increasingly prominent until four months before admission when because of this illness he could no longer work. For three months he had been confined to bed most of the time. He had lost 16 pounds of weight and had a poor appetite. Acetylsalicylic acid in doses of 0.64 gm. two or three times a day lessened discomfort, heat applied to the back gave partial and temporary relief. Three osteopathic manipulations aggravated the back pain.

He had had measles, mumps and chickenpox during early childhood, there were no symptoms of rheumatic fever, he denied any venereal disease. He had been quite athletic before the present illness.

Physical examination revealed an anxious appearance and obviously pain was experienced during most movements. There was moderate undernutrition. The tonsils had been removed, the teeth were excellent. The heart, lungs and abdomen were negative. The prostate was normal to palpation, the external genitalia were negative. Neurologic examination was negative. There was painless motion through a normal range in the cervical spine. Rotation, lateral bending and forward and backward motions of the spine were limited to 50 per cent of normal in the dorsal region and to 20 per cent of normal in the lumbar segment. There was practically no hyperextension of the lumbar spine which had only a small forward convexity. The back muscles were spastic and quite tender. Percussion over the dorsal and lumbar spinous processes and sacroiliac joints caused considerable pain. All motions of the dorsal and lumbar spine caused pain. Straight leg raising was limited to 50 degrees. All other hip motions were normal. Rising from a supine position was difficult and very painful. When the patient stood with the legs extended at the knees, flexion at the hips was limited so that he could get the finger tips only 10 inches from the floor. Expansion of the chest was limited to 1½ inches measured at the nipple line.

Laboratory studies showed 12 gm. of hemoglobin, 4.2 million red blood cells, 8200 leukocytes with a normal cell distribution. The corrected erythrocyte sedimentation rate was 1.2 mm. per minute (Rourke-Ernstene). Urine was normal. The spine and pelvis x-rays showed marked thinning of both sacroiliac joint spaces with irregularity of the borders and increased irregularity of the adjacent bone, slight generalized osteoporosis, only small amount of lumbar lordosis. The hip joints and lumbar facets appeared normal, there was no spinous ligament calcification.

Diagnosis: Early spondylitis rhizomélhique (Marie-Strumpell)

The patient was treated with x-rays according to the following plan. The back was divided into portals as indicated in Figure 95. Ports 1, 3 and 5 were treated on the first, third and fifth days of therapy and ports 2 and 4, on the second, fourth and seventh days. Each port received 200 r (measured in air) each day it was treated so that a total of 600 r was administered through each portal. The factors were 200 KV (175 KV constant potential equivalent), 0.5 mm. of copper and 1.0 mm. aluminum filtration, a half valve layer of 0.9 mm. of copper, 50 cm. skin-target distance and an output of 50 r (measured in air) per minute. During the latter part of treatment and for three days afterward there was considerable nausea and anorexia, but no vomiting. Beginning the week following treatment pain gradually lessened and increase in back motions was noted by

the patient and the examiner. No other treatment was given except acetylsalicylic acid such as he had been taking for many months. He was discharged home, advised to be up and about and exercise as he felt capable and comfortable in doing.

When the patient returned four weeks after roentgen therapy had been completed—as was requested—he reported that he had enjoyed increasing comfort and activity, there was only moderate low back pain and slight dorsal back and chest pain and an increase of 4 pounds in weight. Examination revealed greater motion throughout the spine with less pain and tenderness. Chest expansion was $2\frac{1}{2}$ inches and he could reach to within 6 inches of the floor. The leukocyte count was 6000 and the erythrocyte sedimentation rate 0.8 mm. per minute. A second series of x ray treatments was given in exactly the same manner as the first. There was slightly more gastrointestinal discomfort but he did not vomit. At the end of treatment the white blood cell count was 4800. He felt about as he did at the beginning of the second series of treatments. He was discharged with the advice to increase activity as he felt capable of doing.

He returned five weeks later stating that nausea and anorexia disappeared three days after he returned home. He had progressively increasing comfort so that he had only slight low back pain. He began working about the farm and during the two weeks just passed had done 60 to 80 per cent normal activity, comfortably. He had gained 4 pounds more. When examined it was found he had normal dorsal spine motion, slight restriction of lumbar spine motion. Chest expansion was 3 inches. He could reach to within 4 inches of the floor. The leukocyte count was 6400. Erythrocyte sedimentation rate, 0.7 mm. per minute. A third series of x ray treatment was given comparable to the previous two series. The treatment was accompanied by gastrointestinal symptoms about as during the second series.

He returned six weeks after completion of the third series of treatment happy because he was free of back and leg pain. Breathing was unrestricted and comfortable, he was able to do heavy farm work, including driving a tractor. Lifting heavy objects from the ground to higher places was the only activity that caused mild back pain. Examination showed there was normal and painless motion in all parts of the spine. Chest expansion was 3 inches. He could bend forward to touch the floor. Weight had increased two pounds. The leukocyte count was 5500 and erythrocyte sedimentation rate 0.55 mm. per minute. New spinal roentgenograms showed no changes.

This patient continued normal activities unrestricted. He was examined at intervals of approximately three months for the following year then at six month intervals for three more years until the present time. There have been only minor low back pains after unusual work or fatigue. He has continued to be essentially well. The erythrocyte sedimentation rate has fluctuated between 0.4 and 0.6 mm. per minute.

X-rays of the spine have remained unchanged. Moderate tanning of the skin over the portals of treatment gradually disappeared.

Comment on Case I—The results in this patient were indeed excellent and illustrate the benefit that roentgen therapy may provide to patients treated adequately early in the stage of spondylitis rhizomélisque. Unfortunately patients usually present themselves for treatment later in the disease process after a larger extent of the spine has become diseased with x-ray evidence of ankylosed facets or calcification of spinous ligaments. When these irreversible changes have occurred it is of course impossible to mobilize these portions of the spine and all that can be gained by x-ray therapy in these cases is relief of pain and muscle spasm, the amount of motion that such abnormalities impose may be gained, but no more. In our last report¹⁸ an analysis of fifty-two cases was presented. Of this group the thirteen patients who had early disease as indicated by x-ray changes being limited to sacroiliac joints, 92 per cent received good, excellent, or complete symptomatic relief of pain and stiffness and a corresponding degree of improvement of spine, hip, and chest motions and other objective evidences of improvement. Of the nineteen cases classified as moderately advanced in the disease, with more extensive sacroiliac disease and incomplete calcification of spinous ligaments, 68 per cent were improved significantly symptomatically and 37 per cent objectively. There were twenty cases in which the disease was far advanced and of these 65 per cent were significantly improved subjectively and 35 per cent objectively. When the results were analyzed in relation to the duration of symptoms and signs of the disease, the degree and incidence of symptomatic and objective improvement was similar to the above figures.

Since this report we have carefully studied seventy additional cases of this type of spondylitis treated by roentgen radiation for a minimum of a year after treatment was instituted and the results have continued to be essentially as in the earlier group. Because of the fact that approximately half of the patients treated with the technic employed in Case I were uncomfortable with gastrointestinal irritation during and following treatment and a few had leukopenia, we have varied the treatment schedule and factors in different ways trying to find the best technic. The plan which now appears to give best results is exemplified in the following case.

Case II. Spondylitis Rhizomélisque; X-Ray Treatment with Modified Technic; Supplementary Vitamins

W. E., a white, married man aged 42, complained of pain in the back and shoulders. He had been well until five years previously when he had a coronary occlusion proven by electrocardiographic studies. This healed uneventually, several months later he noticed pain in the lower back which at times would radiate down both legs in sciatic distribution. Soon thereafter he was studied in a large

teaching hospital where it was considered he had gout. Treatment with colchicine was not beneficial. He continued to have aching pain and stiffness which gradually spread upward in the back. Pain and swelling developed at the ankles, feet and sternoclavicular articulations. Two years previously he spent the winter months in an Arizona sanatorium where the diagnosis "atrophic arthritis" was made and treatments with vaccine and physical therapy were given with moderate improvement in the extremity joints. He returned to his Ohio home where he resumed work which included much automobile and train travel. The jarring of travel aggravated the back pain. During the year previous the extremity joints gradually returned to essentially normal and the low back pain lessened, but pain in the dorsal back increased and spread to involve the neck and shoulders. Sneezing and coughing caused excruciating pain in the back and at the sternocostal cartilages. Chest expansion became difficult and forward bending of the back became limited. He lost 5 pounds of weight. A Taylor type back brace had been worn for eight months with slight improvement.

Examination revealed a stooped posture. He walked with a stiff back and neck and was in moderate discomfort. The back moved as one piece from the shoulders to the sacrum. There was loss of lumbar curve. Attempts to move the spine caused painful spasm of the back muscles. There was practically no lateral flexion of the spine, no extension in the lumbar portion. Rotation of the dorsal and lumbar spine was limited to 10 degrees to right and left and was moderately painful. Chest expansion was limited to 2 inches measured at the nipple line, at the end of expansion there was considerable costosternal discomfort. Forward bending while standing with straight legs was limited so he could come to within only 18 inches of the floor. The remainder of the examination was negative.

Hematologic examination was normal with a white blood cell count of 9800, the erythrocyte sedimentation rate was 78 mm per hour (Westergren method). Roentgenograms showed almost complete ankylosis of the sacroiliac joints, moderate calcification of the right lateral longitudinal spinal ligaments between the fourth and fifth lumbar vertebrae and of the left lateral ligament between the second and third lumbar vertebrae, and slight calcification laterally between the eleventh and twelfth dorsal left and the eighth, ninth and tenth dorsal right. No calcification was observed in the anterior ligaments in the lumbar and dorsal back; the posterior articulations were irregular with moderate cartilage decrease but none were ankylosed. The cervical spine appeared normal except for slight and incomplete calcification in the anterior ligament between the sixth and seventh cervical vertebrae.

The back was treated with roentgen radiation to ports as shown in Figure 96. The physical factors were KV 140, M.A. 10, distance T.S.D. 50 cm, filters 0.5 copper, 1 mm. aluminum. Each port received 150 r \times 3—a total of 450 r. Only two ports were treated each day. There was much nausea and anorexia during the last two days of treatment. The leukocyte count did not change. At the end of treatment there was less pain in the neck and shoulders and motion of the shoulders was no longer painful. The patient was discharged.

Five weeks later the patient returned and reported progressive decrease in pain and stiffness of the back, shoulders and chest since roentgen therapy. Anorexia lasted two weeks after x-ray treatment, thereafter appetite became excellent. There was completely normal and painless motion in the cervical spine and shoulders. The dorsal lumbar spine could be moved 10 degrees laterally to right and left,

in rotation, 15 degrees to right and 20 degrees, left. There was slight stretching type of pain. Chest expansion was $2\frac{1}{2}$ inches with only slight pain at the end of deep inspiration. Forward bending was possible to within $15\frac{1}{2}$ inches from the floor. Percussion over the back caused no pain. The white blood cell count was 5800, the erythrocyte sedimentation rate 42 mm per hour.

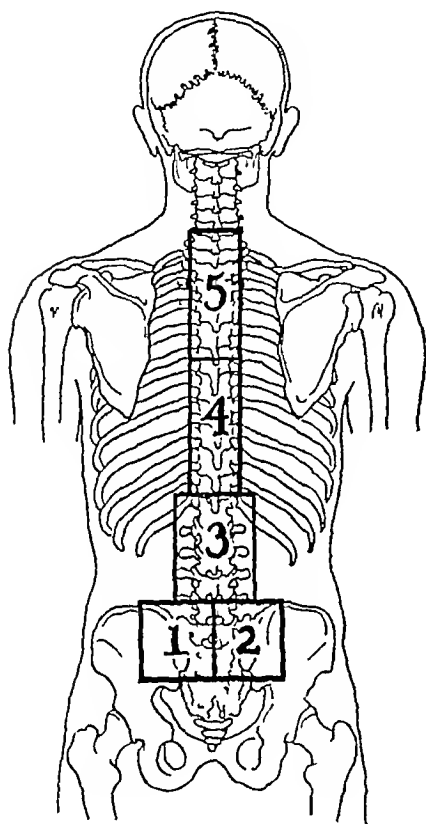


Fig 95

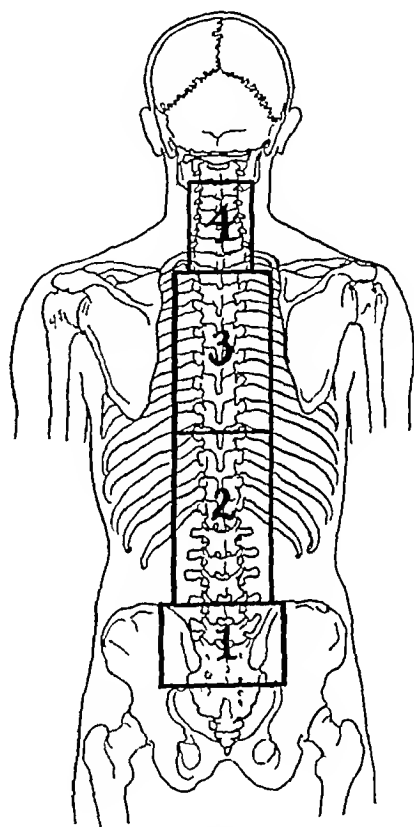


Fig 96

Fig 95—The ports of irradiation customarily used during earlier studies. Fields 1 and 2 measured approximately 12 by 14 cm, field 3, 16 by 14 cm, fields 4 and 5, 18 by 10 cm.

Fig 96—Wider ports of irradiation as shown in this diagram irradiated with smaller doses of x-rays appears advantageous. Field 1 is usually 12 by 18 cm., field 2 and 3, 18 by 16 cm, field 4, 14 by 12 cm.

Roentgen therapy was again administered exactly as it was formerly. During this treatment thiamine hydrochloride was given orally, 10 mg three times a day. Slight anorexia occurred on the fourth day of treatment. On the fourth, fifth and sixth treatment days, 100 mg of pyridoxine was injected intravenously. The anorexia lessened on the fifth day and disappeared the day after therapy was finished. Neither nausea nor emesis occurred. The patient felt distinctly more comfort-

able throughout treatment. Back pain and stiffness lessened. The patient stopped wearing the brace and has not worn it since that time.

Six weeks later the same areas of the back were again treated but to each port only 100 r \times 3 were given. There was no disturbance of any sort during this series of treatments. The patient continued to improve and returned four months later stating he felt free of pain for the three months previously. He had played nine to twelve holes of golf daily without discomfort except for slight lumbar back pain on rare occasions. He was active at an executive position in business daily. Back motions were Cervical, normal, dorsolumbar lateral motion 15 degrees right, 10 degrees left, rotation 25 degrees to right and left, and 15 degrees extension of the lumbar region. Forward flexion was to within 14 inches of the floor. There was no pain. Chest expansion, 3 inches. The white blood cell count was 7400, the erythrocyte sedimentation rate, 25 mm. per hour. Because he was so well and essentially asymptomatic no more roentgen therapy was advised.

Five months later the patient was reexamined. He had felt "fine" during the interval and was busy at work and increasing social and recreational activities. He had gained 15 pounds in excess weight. Back motions were entirely painless and had increased to 30 degrees rotation both to the right and left and 15 degrees lateral motion of dorsolumbar spine, there was 50 per cent normal extension of the lumbar back, forward bending to 10 inches from the floor. Cervical spine motion remained normal and painless. Chest expansion was 3 inches. The patient was advised to reduce his weight to normal. No other treatment was considered necessary.

PRACTICAL CONSIDERATIONS OF ROENTGEN THERAPY FOR SPONDYLITIS RHIZOMÉLIQUE

As did the first patient, W. E. (Case II) also showed excellent improvement during treatment, which continued to date—almost a year since treatment was finished. It should be noted that there were these differences. In the second patient the voltage was lower, the ports were wider so that more of the paraspinous tissue was irradiated and the roentgen dosage was smaller. With this technic our results have been quite as good in relieving the pain and stiffness of spondylitis and the gastrointestinal sickness has been distinctly less frequent and less severe. Thiamine hydrochloride is not given routinely during treatment but when considerable anorexia or nausea occurs it is begun 10 or 15 mg. orally three times a day and used throughout subsequent treatment periods. In several patients there has been less gastrointestinal disturbance when thiamine was administered. If severe nausea or vomiting occurred pyridoxine, 50 or 100 mg. intravenously daily frequently seemed to lessen these symptoms. Whether

the benefits were a psychic effect or due to a biologic action of the vitamins cannot at present be stated. It seems advisable to use thiamine hydrochloride or pyridoxine in these ways for the practical value which is apparent, until there is better prophylaxis or treatment for these disturbing complications of roentgen therapy.

Since using the technic with lower voltage and reduced roentgen dosage, leukopenia has been encountered only rarely and only when treatment was given repeatedly over the entire spinal column. White blood cell counts below 3000 have not been observed. If gradual decrease in leukocytes develops, treatment is slowed a bit—usually lengthening the interval to three days between successive irradiation treatments to the same port. Anorexia has not been observed after treatment with the technic we have employed.

Tanning of the skin has not been objectionable. Patients are advised not to take sun baths or have ultraviolet light treatments during or for a few weeks after roentgen therapy to the back. Because of the depilatory effects of x-rays the cervical region is not treated above the hair line of the scalp.

It is fortunate that this disease occurs chiefly in males for roentgen therapy over the pelvis may suppress the function of the ovaries. This must be kept in mind in treating female patients in the child bearing period. Because each ovary lies close to the roof of the acetabulum irradiation of the hips especially must be done cautiously and with reduced dosage if it is used. Although potentially less dangerous, similar caution must be exercised in treating the sacroiliac regions in female patients. With the technical factors we have employed no effects on male gonads have been observed.

The manner in which x-ray therapy produces benefit in patients with spondylitis rhizomélisque is not clear. It seems apparent that results depend not only upon irradiation of the spine and its joints and longitudinal ligaments, but upon irradiation of back muscles and their attachments to the spine, thus is the reason wider fields are now being employed.

If roentgenographic evidence of disease is confined to the sacroiliac joints or to these joints and the lumbar spine, and if pain, stiffness and limited motion extend no higher than the lumbar or low dorsal region, roentgen treatment is given only to these parts and a margin of several segments above the level of obvious clinical involvement. If the symptoms or signs exist in most or all of the back, treatment is directed to the entire spine and paraspinous tissues. When hip or shoulders are affected additional ports are chosen to cover these articulations and the posterior muscle groups about them are irradiated. If extensive calcification of ligaments of the spine or ankylosis of joints has occurred, roentgen therapy cannot mobilize these parts. In such cases all that can be accomplished from roentgen therapy is the relief of back pain due to the muscle stiffness and spasm.

Those patients who have ankylosis with extensive ligamentous calcification in the late stage of the disease and who have little or no pain, will not benefit from roentgen therapy, and it should not be employed. Frequently patients are encountered in whom the disease process is long standing in the low back where ankylosis has occurred and pain no longer exists, but the disease is younger in the upper dorsal region, neck or shoulders. In this situation treatment has been directed to the upper back and shoulders only, often with good relief of pain and stiffness and increase in motion.

One cannot be didactic regarding the amount of treatment to use. Our results indicate that if two series of treatments do not effect improvement, more roentgen therapy cannot be expected to be beneficial. If benefit is observed during earlier treatments three series of treatments are given at four or six week intervals. If, at the time the third series of treatments is started, there is only slight residual pain and stiffness the dosage is reduced as illustrated in Case II, otherwise, the full roentgen dose is given. After the third series of treatments the patients may need no more therapy for months. Many cases treated early in the disease have gone for as long as four or five years (to the time of this writing) without needing more treatment—the patients remaining comfortable in full activity without signs of progression of the disease. Others after several months may have recurrence of pain or stiffness and limited motion. As soon as this is recognized more x ray treatment—100 or 150 r repeated once or twice at the site of symptoms—often brings prompt relief. Thus subsequent treatment may be needed at irregular intervals to maintain best results.

A question of paramount importance is whether or not roentgen therapy arrests the disease process or whether it effects analgesia only. Evidence is as yet insufficient to answer this question. Several of our patients who have been treated with x ray early in the disease process have for the several years since treatment shown no sign of progression of the disease. However, it is well known that spondylitis of this type may progress to different levels of the back and remain quiescent thereafter in the natural course of the disease. Furthermore, it is known that some patients have bilateral sacroileitis and do not develop arthritis of the spine above the pelvis. Those patients who have roentgenographic evidence of bilateral sacroiliac arthritis without other roentgen sign of disease, but who have painful spasm of back muscles, decreased motion of the lumbar and dorsal back, diminished and painful breathing and signs of general illness with elevated sedimentation rate we believe have spinal arthritis. When all clinical evidence of disease disappears and the erythrocyte sedimentation rate returns to or toward normal as it has done in some cases shortly after x-ray therapy, one wonders if this does not represent arrest of the disease process. However, until more is known concerning the nature of the disease its etiology, the manner of action of x-ray therapy and until

a much larger group of cases has been observed for ten or twenty years after treatment, this question will need to go unanswered. It seems very certain, however, that roentgen therapy is the most dependable means of relieving the discomfort of this disease and if that can be accomplished the patient is most appreciative. Analgesia is apparently the result, largely at least, of relief of painful muscle spasm. The increment of stiffness due to spasm, and the impairment of motion therefrom, are thus released and function improves correspondingly.

The speed with which the benefits of x-ray therapy occur should be emphasized. Frequently within one or two weeks after treatment is begun there is definite benefit, and often within a total of two months patients go quite comfortably about their usual activities. No other type of treatment in my experience has produced such good results so quickly. Another extremely important aspect is the freedom from encumbrances to spine motion during this form of therapy. The value of planned exercises of extremity joints involved with rheumatoid arthritis and the disastrous results with ankylosis, which may occur rapidly if such joints are encased in plaster and motion prevented, are generally appreciated. It seems quite analogous that if the spine is kept rigidly braced or motionless in plaster, ankylosis will be favored. If roentgen therapy serves no other purpose than to relieve pain and muscle spasm it is quite desirable that these benefits be accomplished while the patient is free to exercise the back and prevent the development of inevitable stiffness. I avoid the use of braces and other means of fixation whenever possible for these reasons and, as soon as pain is sufficiently relieved, I advise systematic exercises for involved joints.

Follow-up roentgenograms never show lessening of ligament calcification or ankylosis even though clinical results have been good. Increase in ligament calcification may even be observed. This calcification appears to follow damages of inflammation occurring in earlier stages of the disease process, and thus may extend after symptoms have been relieved, especially if motion cannot be materially increased.

ROENTGEN THERAPY IN OTHER RHEUMATIC CONDITIONS

Rheumatoid Arthritis.—With good results the rule in spondylitis rhizomélisque, one would expect roentgen therapy to be of value in the treatment of rheumatoid arthritis of extremity joints, for most rheumatologists consider that pathology of the spinal and extremity joint inflammation similar if not identical. However, with treatment similar to that described for spondylitis, our results in many cases of rheumatoid arthritis have been poor. In the report of 1941¹² summarizing fifty-seven cases we stated “— in patients with rheumatoid arthritis roentgen irradiation by the technique employed gave unpredictable and unreliable results, which by careful study were shown to be far less satisfactory than other reports have suggested, and in general they

were so discouraging that we have abandoned this treatment except in rare, obstinate cases or cases in which a psychic effect is desired." With four additional years our observations and conclusions remain the same. It should be emphasized, however, that in all of our patients the treatment has followed the same pattern as that which gave quite good results in spondylitis. With different technic better results might occur. Borak and Taylor¹⁴ recently reported beneficial effects of roentgen therapy in advanced cases of rheumatoid arthritis, in whom a variety of other forms of treatment had failed to arrest the disease process. The x-ray therapy used by these authors was considerably different than that we have employed especially in that the more chronic cases were irradiated more persistently and larger total roentgen dosages were given to each port—"usually between 800 and 1,600 r." They state that as the joint disease advances through stages first of edema, inflammation and hyperplasia of synovial membrane, then granulomatous and fibrous tissue, and lastly cartilage destruction and ankylosis, "to obtain comparable effects, larger doses of x-rays are required in the more advanced stages." The authors "feel that the use of roentgen therapy is justified in certain cases of advanced rheumatoid arthritis" and in their summary state that "roentgen therapy is given for the relief of local symptoms, to alleviate pain, and increase mobility, and is employed only after failure of the usually accepted methods of treatment."

The most important theoretical and practical criticism of treatment of diseased joint in cases of rheumatoid arthritis is that local treatment is being administered for a constitutional disease. It could not therefore be complete therapy, it could only serve as an adjunct in treatment. We have been disappointed with its use in this role.

Osteoarthritis—Many more patients with osteoarthritis have been treated since our earlier report. These patients for the most part were suffering from pain and stiffness at the hips (*malum coxae senilis*) and at the spine. Roentgenograms showed characteristic changes. For the hips, treatment was always given to anterior and posterior ports, and often a lateral port was used in addition. Dosage would usually be $200\text{ r} \times 3$, or $150\text{ r} \times 3$ to each port in each series of treatments. Even though two or three series would be used, invariably treatment to the hips gave poor results. In some cases slight temporary relief from pain was reported, but in most instances no subjective or objective benefit was noted.

Osteoarthritis of the spine was treated in a manner similar to that used in cases of spondylitis rhizomélisque. Results were on the whole poor. Sometimes there was considerable relief of pain and stiffness. The better results were noted in those patients with considerable soreness and tenderness or spasm of back muscles, and it was felt that the relief, when it occurred, was due to a beneficial effect on the "secondary fibrositis" rather than on the joint disease.

Nonarticular Rheumatism—Effects of roentgen therapy have been observed in a group of cases with different forms of nonarticular rheumatism. A critical analysis of results in these cases will not at this time be presented. Certain generalizations are warranted on the basis of our results thus far. Patients who had chiefly or only fibrositis of the back, usually at the lumbar and sacral, or the interscapular and cervical regions, received treatment to the involved areas with the technic used in treating spondylitis except that often the dosage was 100 or 75 r \times 3. Approximately 50 per cent of these patients received no benefit. In the remainder, relief of pain and stiffness was noted but seldom was it impressive or lasting. In a few patients with rather localized disease, results were sufficiently good to consider the process satisfactorily controlled.

Patients with *acute*, subacromial bursitis were seldom helped by x-ray treatment to the bursa. Several experienced increased pain probably because of increase in edema and stretching of the bursal wall, already distended from the inflammation. Approximately 30 per cent of patients with "periarthrits of the shoulder" which might follow bursitis or occur independently—fibrositis of the shoulder—were relieved of pain following roentgen therapy when radiation was given over wide anterior and posterior ports if treated before the late stage of severe limitation of motion. Exercise, both active and assisted, was always instituted in addition to roentgen treatment, and is considered necessary for best results.

In about half of the cases of ischial, trochanteric or Achilles bursitis, painful attachment of tendons at the humeral epicondyle, femoral trochanter or calcaneus, and palmar or plantar fasciitis have significant relief of pain and cessation of symptoms followed x-ray therapy usually with 100 r \times 3 repeated once or twice at three or four week intervals, to one or two ports as needed to irradiate all tissue in each lesion.

SUMMARY

By the methods used, roentgen treatment has given better and quicker relief of pain and stiffness in spondylitis rhizomélisque than any other form of treatment. In the majority of cases benefit has persisted for as long as these cases have been followed—up to six years. Better results are usually obtained the earlier treatment is instituted in the course of the disease process. X-ray treatment for other forms of rheumatic disease has been less beneficial—for rheumatoid arthritis of extremity joints it has been unreliable, it has failed in almost all cases of osteoarthritis. In some patients with nonarticular rheumatism relief has quickly followed roentgen therapy, especially in cases of subacute bursitis, fasciitis and tendon attachment pain. Roentgen treatment should be considered as part of the therapeutic program for certain forms of rheumatism but it should be wisely administered and its limitations appreciated.

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THE USE OF VITAMINS IN THE TREATMENT OF CHRONIC ARTHRITIS

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Physicians and the laity have over the past years been deluged with propaganda recommending vitamins for all manner of diseases. It is not surprising, therefore, that vitamins have been recommended for the treatment of chronic arthritis. The use of vitamins in the treatment of arthritis was thoroughly surveyed by Freyberg in 1942, and since then no important contributions to this subject have been reported.

Considering the vitamins *seriatim*, *vitamin A* has no proven place in the therapy of chronic arthritis. Patients have been given large doses of vitamin A by several investigators without any appreciable effect on the severity or course of the disease.

VITAMIN B COMPLEX

Regarding the vitamin B complex, we shall discuss only thiamine hydrochloride, riboflavin, niacin, and niacinamide. The many other elements which make up the vitamin B complex have not yet proved themselves to be of any importance in arthritis.

In 1922 A. A. Fletcher suggested that a vitamin B deficiency might be related in the development of certain features of rheumatoid arthritis. He reported atony of the intestinal musculature with redundancy of the large bowel which was alleviated by feeding the patients wheat germ and assumed that there might be a causal relationship between the digestive system and chronic arthritis, that some digestive disturbance such as constipation, diarrhea or putrefaction might be involved in the onset of joint disease or parallel its severity.

The writer, together with R. G. Snyder, several years ago studied the colons of some thirty patients with chronic arthritis roentgenologically, all of whom were subsequently treated with large doses of vitamin B complex in the form of yeast, bemax. None of these patients was benefited in the least insofar as his arthritic symptoms were concerned, and five of them showed a definite increase in the size of the colon. Many of them complained of abdominal discomfort and excessive gas. We considered useless the use of yeast and wheat germ as a treatment for intestinal atony with or without arthritis.

The use of *thiamine hydrochloride* in large doses for the treatment of neuritis has received a great deal of attention in the literature.

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Many forms of rheumatoid arthritis involve the para articular and periarticular structures, and are often accompanied by neuritic disturbances. It has been our experience that the use of thiamine hydrochloride has never been specific in the alleviation of these neuritic pains.

Niacin, administered orally or parenterally, produces a transient flushing phenomenon which frequently brought temporary relief of joint pain. In this respect, however, it does not differ in its effects from the application of local heat by the use of hot water bottles or electric pads, or hot baths—or any other heat producing modality.

Kurtz reported significant subjective and objective improvement in 75 per cent of an unselected group of rheumatoid arthritic cases treated with intravenous and oral administration of nicotinic acid in doses large enough to produce definite and prolonged flushing of the skin.

Our experience is that such improvement is only very temporary—and the degree of relief obtained is out of proportion to the expense and the effort involved.

Niacinamide and *riboflavin* have no established place in the therapy of chronic arthritis in any of its forms. It is quite true that a great many patients suffering from rheumatoid arthritis are generally debilitated and suffer from anorexia in various degrees. In these patients, the use of vitamin B complex as a tonic is a rational procedure, and should be considered as a useful and important adjunct in the treatment of this disease.

VITAMIN C

Joint disease and lesions have frequently been found in persons afflicted with scurvy. Many investigators have tried to prove a relationship between a vitamin C deficiency and the course and progress of chronic arthritis. In 1935, Rinehart reported several cases of subacute or chronic vitamin C deficiency in guinea pigs which produced an arthropathy with manifold similarities to rheumatoid arthritis. In 1939 he reported a detailed study of the nutritional status relative to vitamin C in a series of cases of rheumatoid spondylitis. He concluded that vitamin C deficiency was almost uniformly present in this form of arthritis and that this deficiency might occur in the presence of a normally adequate vitamin C intake. The uniform vitamin C depletion and the response to the liberal vitamin C supplement suggested that the deficiency was contributory to the disease.

In 1939 Hall, Darling and Taylor studied the ascorbic acid content of the blood serum in fifty-eight unselected cases of rheumatoid arthritis and found low values in most cases. All of these patients were receiving a normal hospital diet containing 80 mg of ascorbic acid daily. Their study appeared to indicate that in rheumatoid arthritis there is an increased requirement of vitamin C. All of the patients therefore, were given extra doses of vitamin C with the hospital diets but

no clinical improvement of the arthritis attributable to the vitamin C treatment was reported

Rutt in 1940 reported on forty-seven patients with rheumatoid arthritis who had very low values for blood ascorbic acid, forty-five of whom showed medium increase of this value after intravenous injections of 100 mg of ascorbic acid daily. Some cases were observed for as long as six months and, although the plasma ascorbic acid values increased to normal levels and remained high, there was no decrease in sedimentation rates, and no noticeable effect on the clinical condition or joint changes.

Freyberg in 1942 measured the ascorbic acid content of the blood of more than 100 patients with arthritis of the rheumatoid type, and reported that the majority of the patients showed abnormally low values of plasma ascorbic acid. He found no relationship between the severity of the arthritis and the blood ascorbic acid content. Large supplements of ascorbic acid were given daily, either as natural fruit juices, or as pure ascorbic acid in amounts sufficient to maintain normal vitamin C level. Repeated demonstrations were observed over long periods of time, there was no evidence that the severity or the course of the disease was in any way affected by this treatment.

Large doses of vitamin C have been used in conjunction with gold therapy in the treatment of chronic arthritis in the hope that such additional vitamin therapy would tend to prevent the toxic reactions which occasionally accompany gold therapy. However, it is our experience that vitamin C is of no value in this connection.

VITAMIN D

Because of its importance in the treatment of rickets, a disease of the bones, it seemed only natural to think that vitamin D deficiency might be in some manner associated with chronic arthritis. The idea that massive doses of vitamin D might be important in the treatment of arthritis was founded on a chance observation made by Dreyer and Reed in 1935. They found that massive doses of vitamin D administered to patients suffering from hay fever resulted in a definite improvement of the arthritic condition with which two hay fever patients were afflicted. This accidental finding gave rise to a widespread investigation by many physicians in many centers in this country, with conflicting results, with the consequence that the Council of Pharmacology and Chemistry of the American Medical Association in 1939 condemned all high-potency vitamin D preparations as "being of little therapeutic value, and their use is not without danger." In our own experience in the Arthritis Clinic at the Hospital for Special Surgery (Ruptured and Crippled) we have used massive dosage vitamin D therapy in several hundred cases. Because of the numerous conflicting reports by various investigators, this type of treatment was studied from the standpoint of efficacy, dosage and toxicity. A small group of

twenty-three "refractory" cases (in which at least one of the prevailing accepted forms of therapy had failed) were treated to determine the optimum dosage and the mode of administration. It was found that from 3 to 6 capsules, representing 150,000 to 300,000 units of vitamin D, could be employed with relative safety. Frequent laboratory studies were made, including blood calcium and phosphorus determinations, blood counts, urinalyses and roentgenological studies of the involved joints. Symptoms of toxicity were found to be limited to slight nausea, heartburn and headache—all of which were alleviated when the dosage was reduced in amount or when the medication was temporarily withdrawn.

More extensive observations were made in a group of 200 cases of chronic arthritis in which the effects on the renal, digestive and circulatory systems were studied. Frequent blood examinations, periodic x-ray studies, and liver function tests were made. About fifty of these cases were followed for a six-year period to determine the possibility of toxicity from the prolonged use of massive dosages of Vitamin D. Subjective improvement occurred frequently, and, to be sure, much more frequently than objective improvement. In some cases patients definitely showed significant subjective and objective improvement. Both, however, occurred slowly. Three or four months may be required before any evidence of improvement is noticeable. Some of these patients have remained symptom-free without any recurrence after a complete cessation of the drug for as long as two years. There have been, of course, some cases of recurrence. Two cases of periarticular deposits of calcium in the soft tissue were seen in which hypercalcemia was present. In one of these cases the calcium deposit disappeared when the medication was discontinued.

Our experience coincides with that of Freyberg that the improvement in this type of therapy was not psychogenic because we both used placebo preparations which were identical in appearance with the regular product. None of these patients reported any subjective or objective treatment.

We used only the electrically activated vaporized sterol Whittier process* in this clinical study. Because other investigators using other forms of massive dosage of vitamin D therapy reported that their use was unsuccessful in the treatment of arthritis, we treated cases with ultraviolet irradiated vitamin D (Steenbock process). This latter preparation proved to be not nearly so effective and toxic symptoms were more frequent and more pronounced. More recently, in the past three years, we have used a parenteral form of the Whittier process vitamin D in weekly dosages ranging from half a million to one and a half million units. We have never encountered any instance of gastric disturbances, headache or other signs of toxicity with the parenteral form of therapy.

* Eritron.

We are now using parenteral and oral therapy, and find this combination to be safe and nontoxic. The use of massive dosages in vitamin D therapy is, of course, completely empirical, but the same may be said of any type of therapy directed against chronic arthritis.

Reports of toxicity from massive dosages in vitamin D therapy have been reported from time to time in the literature, but it is not nearly as toxic as the various forms of gold therapy. It has been suggested that the therapeutically useful ingredient of vitamin D may not even be vitamin D itself but some hitherto undiscovered fraction thereof, probably steroid in nature, and that this substance is preserved in the preparation of vitamin D by the Whittier process, and might possibly be destroyed or altered in the preparation of the other forms of vitamin D products. Of course, this is all highly speculative and further studies are being made in the attempt to solve this problem.

As the result of the treatment with vitamin D of some 500 patients with chronic arthritis over a period of eight years, we have come to the following conclusions:

The medication is a relatively nontoxic therapeutic agent, and is beneficial in the treatment of chronic arthritis of the rheumatoid type. Intolerance occasionally occurs but is easily controlled by reducing the dosage or discontinuing the medication temporarily. Demonstrable signs of improvement are definitely noted, and are frequently sustained even after cessation of medication. There is no increase of calcification of the blood vessels observed either roentgenologically or by ophthalmological examination of the retinal vessels. The renal function is not impaired, as was demonstrated by urinalysis and nonprotein nitrogen determinations. Gallbladder and liver function are not impaired, as was demonstrated by numerous repeated liver function tests and roentgenological studies of the gallbladder with dye. There is no causal relationship between an occasional elevation of blood calcium and vitamin D toxicity.

VITAMIN E

Evans and Burr first pointed out in 1928 that a deficiency in vitamin E may be associated with the development of spastic paralysis and with muscular atrophy in rats. Several investigators reported various types of changes in the skeletal muscles of patients on vitamin E deficient diet. Stone reported a series of rheumatoid arthritis cases with improvement in almost all the female cases and three male cases of Marie-Strumpell arthritis on wheat germ oil.

The first report on the treatment of fibrositis was by Steinberg in 1941. He reported thirty cases of a so-called "primary" fibrositis, with complete relief of all symptoms by oral doses of wheat germ oil, administered over a short period of time. Ingham reported twelve cases of primary fibrositis in all of which the patients recovered completely.

with oral vitamin E therapy. Later in 1942 Steinberg reported another group of twenty patients with primary fibrositis, all of whom were completely relieved by oral vitamin E. Ten cases of secondary fibrositis were not improved. In the same year (1942) he reported forty-eight cases of primary fibrositis cured, twenty-eight with wheat germ oil, twenty with mixed tocopherols, sixty cases of secondary fibrositis did not improve. In July, 1943 he reported on 145 cases with improvement with mixed tocopherols.

In 1945 Morris Ant reported thirty-two cases of so-called primary fibrositis of which he treated nineteen with vitamin E in the form of ointment, six with oral therapy and ointment, and four with high vitamin E diet. He treated two with oral vitamin E alone using mixed tocopherols. There were eight females and twenty-four males. He reported improvement in 70 per cent of the cases treated with the ointment alone. The other 30 per cent was only fair. He concluded that the ointment alone was just as efficacious. Unfortunately, our experience with vitamin E in the form of either wheat germ, wheat germ oil, or the mixed tocopherols did not confirm these reports. Until more controlled studies in the treatment of fibrositis are conducted, the value of this particular vitamin must be considered as questionable.

VITAMIN K

Vitamin K is of importance only in the consideration of therapy of chronic arthritis with respect to the use of salicylates in the treatment of this disease. There is no question that salicylates form an extremely important medication for the relief of pain attending rheumatic fever or rheumatoid arthritis, and that frequently large doses must be employed. The use of such large doses of salicylates may produce toxic manifestations. Depression of the plasma prothrombin level and widespread capillary hemorrhage have been reported as a result of intensive salicylate therapy.

It has been suggested that patients receiving large doses of salicylates over prolonged periods of time should receive concurrently adequate doses of vitamin K. We have never encountered in our own experience a single instance of salicylate toxicity although we have used large dosages over prolonged periods.

CONCLUSIONS

The role of vitamins in the treatment of chronic arthritis is unquestionably not specific, but only supportive and in the case of vitamin D, empirical but definitely useful. There seems to be no direct indication for the use of vitamin A, vitamin B complex (thiamine hydrochloride, niacin, riboflavin) vitamins C, E or K in the relief of symptoms of chronic arthritis.

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PHYSICAL THERAPY IN CHRONIC ARTHRITIS

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PHYSICAL therapeutic measures have been employed since ancient times for alleviating pain and restoring function in rheumatic conditions, as documented by the use of baths and massage many centuries before the Christian era. The laity have instinctively clung to spa treatment for their rheumatic ailments during the recent decades when so much effort has been expended to evolve some specific treatment of rheumatism by vaccines, foreign proteins, various drugs and by the very often indiscriminate removal of suspected foci of infection. Physical medicine not only has stood its ground during all this period, but has come decidedly to the fore in recent years when it was reaffirmed that the functions of the body can be influenced as much from without by physical methods as from the inside by pharmaceutical methods. The dean of modern American pharmacology, Torald Sollmann,¹ stated a few years ago that "Although drug therapy and drugless therapy may seem direct antipodes to the superficial thinker, they involve the same principles evoke the same phenomena, accomplish the same results. They differ only in the means which they employ, of which sometimes the one sometimes the other is better adapted to secure the desired end. Indeed, the differences between physical therapy and pharmacochemical therapy are no greater than those between radiant and direct heat, or between local and general anesthetics."

The great therapist, the late Bernard Fantus,² stated in one of his last writings that physical therapy is more important in chronic arthritis than medicinal therapy. Pemberton³ asserts that physical measures have probably as much value in the treatment of arthritis in its early stages as any others at our disposal. A much quoted report by Dr. J. Allison Glover⁴ to the British Ministry of Health, 1928, reads "Almost every case of chronic arthritis at some stage of the disease requires physical treatment, usually consisting of the application of heat in some form either alone or together with massage and movement. No scheme of treatment for chronic arthritis can be considered complete unless an extensive range of physical methods of treatment under skilled direction is available. There appears to be a rapidly increasing demand for such treatment."

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Physical therapy does not offer merely a symptomatic treatment for relief of pain, for the resorption of products of inflammation, and for the increase of function. It is held that properly planned and applied physical measures in many instances "alter the reactivity of the entire organism, improve the defense-mechanism of the body and help the individual to fight infection and resist abnormal external stimuli" (Bach⁵)

Unfortunately a large number of medical men believe that no special knowledge and experience are needed for the prescription and application of physical measures. Some of them turn their patients over to a technician without any except the most general instructions, others who have had no more instruction in physical therapy than that given by the salesman of their one piece of apparatus—usually a short wave diathermy machine—proceed to use that apparatus indiscriminately on any patient who comes along. Physical therapy in chronic arthritis is to a large extent a therapy of physiological response and requires careful technic and observation for its evaluation.

The list of physical measures available in chronic arthritis is shown in Table 1. Its length may appear formidable or perplexing to the average physician, but on close study it will show only variations of three basic principles, those of heat, exercise and counterirritation.

TABLE 1—PHYSICAL MEASURES IN CHRONIC ARTHRITIS⁶

Thermal	Thermal and Mechanical
Hot bath	Underwater exercise
Radiant heating	Whirlpool bath
Paraffin bath	Counterirritant
Mud pack	Galvanic current
Hot air douche	Ion transfer with vasodilators
Diathermy, long and short wave	High frequency (Oudin) current
Artificial fever	Ultraviolet rays (mercury vapor lamp)
Mechanical or Functional	Thermal and Counterirritant
Rest	Natural sunlight
Massage	Carbon arc lamp
Exercise, active	Galvanic bath
Exercise, passive	

General or systemic physical measures may serve as part of constitutional therapy for the increase of circulation and metabolism, the promotion of activity of the digestive tract and the correction of faulty body mechanism. Physical measures locally applied serve to prevent and relieve local arthritic changes—pain, stiffness, exudation, muscular atrophy and weakness. There is, of course, often an interplay between general and local effects. The selection of a physical treatment measure and its combination with other therapeutic measures must depend on the type, stage and extent of the arthritis and on the subjective complaints of the patient. The reason for the desirability of a variety or intermittency of physical measures, as well as the combination of

several, is that some patients with chronic arthritis are more responsive to certain physical measures than to others and that certain stimuli lose their effect after a time. It is most desirable in some cases that simpler treatment measures be carried out systematically in the patient's home.

THERMAL MEASURES

No matter what form of heat is administered its immediate effect is purely physical: a rise of temperature in the part to which heating is applied. The primary physical effect will vary according to the form of heat, its intensity, and length of application. It has been shown by Sonne⁷ that with radiant heating maximum tolerance on the surface is 113.9° F., and on the undersurface 117.8° F. With diathermy and short wave diathermy in animal experiments in joints an average rise in temperature of 8° was produced. Corresponding effects in human tissues were corroborated by many clinicians. General body temperature can be elevated with artificial hyperpyrexia to 107° F.

According to the temperature law of Van't Hoff, for every rise of 10° C the rate of oxidation is increased 2.5 times, and thus even temperature changes of tenth of degrees will influence cellular oxidations and exert marked effects on physiological processes. The heat-regulating mechanism of the body endeavors to maintain a constant temperature, and when heat is applied to a part from any external source, the vasomotor mechanism responds with an effort to dissipate the excess heat. There follows an active vasodilatation of the capillaries and a subsequent increase of arterial and venous circulation. Lewis has shown that irritation of the skin releases a histamine-like substance which causes dilatation of the capillaries. This local hyperemia in turn results in an increase of the rate of removal of local tissue products and in stimulation of the local resistive forces, among these an increased phagocytosis. An important therapeutic effect of local heating is that in mild dosage it acts as a sedative on irritative conditions of sensory and motor nerves. Hence the relief given by thermal measures in many painful sensory conditions and in spasm.

When heating is applied at sufficient intensity to a large part of the body or if heat loss from the body is prevented, a rise of body temperature and general changes occur. There is an increase of the circulatory rate and of metabolism, a rise in blood volume and oxygen consumption and a change in the urine, blood and sweat to the alkaline side. The clinical effects of mild general body heating can be summed up as follows: (1) increased heat elimination and profuse perspiration; (2) increased circulation: a rise of the pulse rate in the ratio of about 10 beats for each degree Fahrenheit just as it does in fever; (3) a lowering of blood pressure (in contrast to the effects of cold); (4) increased perspiration; (5) increased elimination through the kidneys. There is a loss of water, salt, urea and other nitrogenous

substances, with a relative excess of alkali remaining in the blood and in the tissues, while there is also a temporary loss of body weight. General nervous sensibility is usually markedly lessened.

The enumerated physiological effects of local and general heating are the basis of the extensive clinical use of the diverse forms of heating in rheumatic conditions.

A table by Fox and Van Breemen⁸ presents a scale extending from stimulation to sedation by external heat—chiefly hydrothermal.

TABLE 2—A SCALE OF SEDATION AND STIMULATION BY EXTERNAL HEAT (FOX AND VAN BREEMEN)

Accelerating or stimulant

- Hyperthermal mud (115° to 120° F)
- High pressure douches, hot or cold (with or without strong manipulation)
- Vapor baths (hot)
- Whirlpool baths
- Brine baths
- Diathermy
- Hot air baths
- Half baths
- Radiation baths (light, heat, ultraviolet)
- Low pressure douches
- Vapor baths
- Pool baths (with or without sedative manipulations)

} All at 93° to 98° F

Retarding or sedative

Hot Baths.—The simplest and most generally available form of partial or general heating of the body is its immersion in hot water. Water has a high specific heat and is a relatively good conductor, hence it will heat the body by direct conduction. A hot water bath causes more rapid rise in body temperature than a hot air bath. An important effect of a water bath is that a body or part immersed in water loses weight and becomes more buoyant. The hot water bath therefore offers the added advantage that after the supporting and relaxing effect of the heat has taken place, the limb can be moved more easily by the patient or by a trained assistant, hot water immersion also allows the combination of heat effect with gentle or vigorous friction by a stream of water, such as is applied in the whirlpool bath.

A hot tub bath is usually taken at a temperature of 100° to 108° F. The temperature of the room in which such a bath is given should be between 70° and 80° F. The temperature of the bath at the start should be minimum and may be quickly raised after the patient has been immersed. The bath is continued for ten minutes to half an hour.

The hot bath is one of the most useful routine measures for home treatment of chronic arthritis. Warren and Lehman⁹ state that even in advanced degenerative arthritis in old persons, a series of hot baths usually results in immediate subsidence of symptoms, a gain of 10 to 15 pounds and a feeling of rejuvenation, they warn about raising the

oral temperature above 101° F during the bath, for it is likely to be followed by faintness, weakness and prostration. They found that, during cold weather, many patients of the older group can be kept quiescent by this procedure when it is used regularly three times a week, and occasionally as often as three times a day or enough to relieve symptoms of an acute exacerbation. If one or several joints are particularly slow in responding the application of additional local heating to these joints is indicated. Age (68 to 75 years) is no contraindication.

Therapeutic Pools—Immersing the body in a large pool of hot water which enables the patient to stand and walk and perform some simple exercises is a valuable aid in treatment of stiffened joints and muscles. According to the temperature of the pool, 96° to 106° F, its effect may range from mild general sedation to marked stimulation besides exerting the much desired relaxing and supporting effect. If it is combined with an underwater douche (hydro massage) a powerful stimulation of skin circulation and some massage action may be produced, while skillful manipulation and directed exercise may greatly help in actually mobilizing stiffened joints. Such treatment exerts also a desirable mental effect by encouraging the patient to use his own efforts to perform movements.

Conductive Heating Devices for Home Use.—Hot water bottles and electric pads are useful as simple emergency measures for relief of pain in rheumatic conditions. Care must be taken not to cause skin burns by their prolonged application. The hot water bottle at times causes painful pressure by its weight, it steadily loses its heat. Electric pads do not cause pressure and maintain an even temperature but this may be dangerously high at times. Measurements have shown that in the ordinary household electric pad the average low temperature is 107.6° F.

The Paraffin Bath—This consists of immersion of the extremities into melted paraffin or the application of this paraffin with a paint brush to the surface of the body. It is a simple and effective means for producing a fairly high degree of surface heating and at the same time the skin remains soft and pliable. Temperature tests have shown the skin temperature in a paraffin bath after the formation of a protective "glove" is around 116° F. The paraffin bath is especially useful in second and third degree cases of chronic arthritis of the hands and feet, in which there is considerable swelling, stiffness and pain. Because of the even distribution of heating it affords a sense of comfort and decrease of swelling more quickly than any other form of heating. When carefully applied this method is also perfectly safe.

Heat Lamps.—Heat lamps and infra red radiators enable simple yet efficient "dry" heat applications at the office and in the home. They have largely replaced the former cumbersome dry baking apparatus and light boxes. For home treatments patients should be instructed

to use these appliances for one-half hour two or three times a day over the affected joints. Such heating should be followed by gentle stroking massage.

In painful acute and subacute conditions, patients can bear only mild radiant heating. In such cases thermostatically controlled heat appliances are of definite value because they can be regulated to furnish a temperature just comfortable to the patient.

Diathermy.—Diathermy is the most efficient procedure of heating the deeper structures and has been satisfactorily used for many years in treating the larger joints and the spine. In osteoarthritis localized in such parts, diathermy is almost specific for local relief of pain, promotion of resorption and restoration of function, it also lends itself easily to combination with other measures. In the frequent bilateral knee involvement of the osteoarthritic type in middle-aged women, diathermy combined with suitable rest usually gives complete relief. In traumatic arthritis, diathermy followed by massage or other mechanical agent is likewise the line of first attack. It should be applied for at least half an hour each time, first daily then three times a week.

Short wave diathermy gives the same clinical results as long-wave diathermy, but its technic is more simple and more safe, the coil field or inductance cable method is valuable for warming up an entire extremity.

Artificial Fever Treatment—Artificial fever treatment by diathermy or other means is indicated only in cases of moderate severity which apparently resist all other forms of treatment. A series of treatments at moderately high temperature (102° to 103° F) seems preferable, some of the good results obtained by a systematic thermal cure in the spas are undoubtedly due to the fever production by the prolonged hot baths.

MECHANICAL MEASURES

Rest—Rest is one of the most important and most frequently overlooked measures in the effective treatment of chronic arthritis. Pain or inflammation, whether of traumatic or of infectious origin, is Nature's way of enforcing rest, which is the first requisite for repair in all joints with pain aggravated by movement. Placing the joint at rest either in bed in the most favorable position or by support in light splints or suitable bandaging is a physical therapeutic measure of prime importance that is not sufficiently often appreciated. Not until a joint at rest is without pain, i e., without inflammation, should it be exercised. Chronic fatigue is considered one of the chief factors in arthritis, therefore general bodily and mental rest are of great importance in the nervous, anemic, overworked patient of the rheumatoid type. Rest should be prescribed systematically, with so many periods daily or one or two entire days a week.

Massage.—Massage combined with suitable exercise is the most readily available measure for stimulation of function. Since arthritic joints are already a seat of an inflammatory process, it is a cardinal rule in arthritis that massage must be gentle and must be carried out in the neighborhood but not immediately over the affected joints. The only massage movement permissible at times over an arthritic joint is the lightest form of stroking. There should be no twisting movement of the joint during massage. The patient should be encouraged to move the joints actively after application of heat and massage. When the help of a skilled technician is not available, the physician should give suitable instruction to family members for massage of a patient confined to the home, thus will enable the patient to receive at least some massage with a measure of success. General body massage is of definite value for overcoming the feeling of fatigue, strengthening the muscular system, stimulating body metabolism and soothing the nervous system.

The application of any form of massage, local or general, should always be preceded by the application of heat, external or penetrating, for it opens the vascular channels, relaxes the parts and enlarges the range of motion. This is the reason for the effectiveness of the combination of heating and gentle massage or exercise enabled by the whirlpool bath and by underwater exercise.

Active Motion.—Active motion must be insisted on in arthritis of the rheumatoid type if fibrous and later bony ankylosis is to be prevented. The safest way of carrying this out is to begin in subacute cases with muscle setting exercises and then start active exercises, first without weightbearing and gradually extending them within the full possible range of motion after the parts have been limbered up by heat and massage. Manipulation of joints in conjunction with massage requires great caution. The patient must receive individualized instruction as to what exercises he can do at home and as to the range of motion he should attempt to attain.

General exercise is invaluable toward effecting body correction in arthritis. Deep breathing and abdominal muscle control exert a beneficial effect on the circulation and functions of the body. For the restoration of function, the gradual use of these joints by corrective exercises and occupational therapy is much preferable to manipulation. In certain cases, exercise on simple apparatus may be useful.

Much of the disturbed physiological function in chronic arthritis can be ascribed to incorrect use of the body in faulty posture. Systematic corrective exercises and rest in the corrected position serve to remedy many of these physiological disturbances; therefore from the very beginning of treatment of arthritis, correction of posture can help materially. Occupational therapy is invaluable for rehabilitating patients in all stages.

THERMAL AND MECHANICAL MEASURES

Hydromassage by a whirl-pool bath softens inflammatory induration and relieves pain and spasm by combination of heat and gentle friction. It may be employed in chronic arthritis affecting several joints of an extremity, for weak and painful feet and in patients with additional myositic and neuritic involvement.

Underwater exercises, originally introduced for the treatment of paralysis, have proved to be quite effective in chronic arthritis for restoring joint function and muscular strength by well-directed exercise and manipulation. In the underwater treatment tank, joints can be put through a range of motion much beyond that achieved outside the water. As a matter of fact, there is danger of overdoing joint exercise in fairly tender joints. Often patients with badly affected hips, knees or ankles, unable to walk, gradually regain that function in the pool. Most patients prefer pool or tank treatments to gymnasium treatments because of the additional mental and physical stimulation. To be truly effective in advanced cases, underwater exercise needs expert guidance and sometimes special equipment for hoisting patients and placing them in the pools comfortably. However, in early cases the thoughtful physician can often devise suitable arrangements for such exercises in simple home surroundings.

COUNTERIRRITANT MEASURES

The *galvanic current* offers a useful adjunct in treatment of chronic arthritis, especially in the atrophic type. The galvanic current brings about prolonged hyperemia of the skin and has some effect on the deeper circulation by reflex or direct penetration. For therapeutic efficiency it is important that as large an amount of current as can be borne be applied for a sufficiently long time, at least a forty-five minute session. The *galvanic bath* offers a combination of mild general heating with the stimulating or "alterative" effect of the current to the skin. It may often serve as an effective alternate measure in institutional treatment especially in polyarthritic cases. Fragrant pine extracts or other resinous substances added to electric baths cause additional skin stimulation.

Ion transfer with vasodilating drugs has come to the fore in recent years in the treatment of traumatic and rheumatic conditions. Histamine and choline compounds, when introduced by ion transfer, penetrate the deeper layers of the skin and exert local as well as systemic effects, they stimulate the parasympathetic nerves and dilate the peripheral vascular system. Mecholyl ion transfer produces a less intense local reaction, it is deposited in the deeper layers of the skin and gradually absorbed, thus its effect lasts for several hours. It is useful in rheumatoid arthritis and neuritis when other measures directed for local relief have failed. Histamine ion transfer brings about a more

vigorous local reaction and is preferable in fibrositis and myositis. Its technic is more simple.

High frequency sparking (Oudin treatment) from the single high voltage terminal of a spark gap diathermy apparatus may give marked relief in diffuse pain of neuritic character and subacute arthritis involving several joints. It should be preceded by external heating.

Ultraviolet radiation from a mercury vapor lamp or from a cold quartz type of lamp furnishes relatively cold radiation, i.e., with elimination of infra red rays. The ultraviolet rays will cause various degrees of the familiar sunburn (erythema). Applied over a painful joint, such a sunburn often acts as a counterirritant and alterative, hence the instinctive desire of many arthritics to expose their painful joints to the sun. Cautious local use of artificial radiation from the sources mentioned may serve as an adjunct or alternate to other physical treatment and should be repeated only after the previous reaction has subsided. Sunburning doses should only be applied to one region and not to the entire body.

Natural sunlight or artificial radiation from a carbon arc lamp represents a combination of infra red and ultraviolet radiation. When applied for general body irradiation in suberythematous doses, it serves as an aid in the constitutional treatment of asthenic arthritics, especially those of the rheumatoid type. The beneficial effects of light therapy are partly attributable to the general tonic effect of ultraviolet irradiation, partly to the thermal effect of the infra red component and perhaps also to the increase of the defensive power of the body by the products of biochemical changes in the skin and their effect through the circulation.

SCHEME OF PHYSICAL TREATMENT

The large number of physical measures described constitutes an invaluable aid in the treatment of chronic arthritis and allows a selection of physical agents to fit almost every type or stage of the disease. It is evident that all these measures must be used in conjunction with a plan of general medical treatment. Some of the treatment measures are strictly institutional procedures but most of them can be applied in the physician's office and some may be carried out under skilled direction in the patient's home.

The grading of arthritis is essential for prognosis, as well as for recording cases and judging benefits of different forms of treatment. Physical measures directed towards improvement of circulation and reduction of swellings will bring about favorable response chiefly in the first two grades of the disease. When one encounters unexpected clinical results in advanced cases, it may be explained by the fact that in chronic arthritis many of the painful processes are located in the periarticular tissues, which respond well to appropriate physical treatment.

In mild and moderate cases of osteoarthritis affecting one or two joints, radiant heat and massage or diathermy and massage should be used. In severe cases or in cases affecting several joints, a course of general heating measures is indicated, this may be done at times in the form of a cure at a spa. Exercises should be carried on regularly in all cases. In "worn out" joints, further wear and tear must be avoided by restriction of activities for a while and by suitable support by elastic bandages, caps or belts.

Early cases of rheumatoid arthritis require mild thermal treatment locally as well as systemically to aid general circulation. Acutely painful joints must have complete rest from the beginning. Early heliotherapy, natural or artificial, is important for general tonic effect. Suitable exercises, general as well as local, are to be instituted early to correct posture and prevent deformities. For local treatment, especially at home, daily use of luminous or infra-red sources is advisable, followed by gentle massage and active exercise. Paraffin baths, whirlpool baths or ion transfer with vasodilating drugs are usually effective in reducing swelling and relieving pain in small joints which do not respond well to simple radiant heating.

SPA TREATMENT

The position of a modern health resort is midway between the home and the hospital. It is not a diagnostic clinic nor a research institution but a place for patients who will be benefited by a combination of physical treatment, climate, diet and psychotherapy. Such a combination is most suitable in many cases of rheumatism, and this is why most health resorts emphasize that they treat arthritis and rheumatic conditions. Some of them even profess to specialize in the handling of such conditions. It is, however, evident that not all types of rheumatism will respond to spa therapy and that no spa treatment method has a specific curative effect on rheumatism. Unless the principal factors in the success of a health resort are available, and no single therapeutic agent is relied on, the sending of a patient to a distant spa will not be justified. The presence of an ideal climate and a well equipped hydrotherapeutic department is not sufficient unless the patient gets the benefit of competent medical direction and trained technical assistance. He must also have suitable hotel accommodations and appropriate diet, and the general atmosphere of the resort must be conducive to rest and relaxation. All of this must be available within his financial means.

So far as the selection of types of rheumatism suitable for spa treatment is concerned, it appears to be the consensus that patients in the active stage of the disease, especially of rheumatoid arthritis, do better at home or at an institution at prolonged rest. The exertion of taking treatments in a spa would far outweigh the possible benefit derived

therefrom. After the acute stage, rheumatoid patients may be sent to a warm, dry region, where, in addition to suitable rest, heliotherapy diet, balneotherapy and hydrotherapy may be carefully applied. Too intense heating must be avoided at all times.

Osteoarthritis is generally more suitable for spa treatment. Patients are usually past middle age, are often overfed and obese and have various degrees of arthritic changes in some of the weight bearing joints. They cannot change their mode of living or the abuse of their joints in their home surroundings. Such patients often do exceedingly well by "taking the cure," which consists of thermal measures, massage, judiciously restricted exercise, suitable diet and rest from business worry or nagging relatives. In addition, any existing strain on the heart and the general circulation can be beneficially influenced and after a sojourn of several weeks these patients return home literally rejuvenated. No wonder that patients of this type return faithfully to their favorite spas for a renewal of the spa regimen and keep comfortable even though roentgenograms of their joints show the usual slow progress of the degenerative changes.

HOME TREATMENT

Because of the essentially chronic course of arthritis and the grave economic problem often created by the length of treatment, increasing emphasis has been laid in recent years on the employment of properly directed home treatment by physical agents. In many cases of chronic arthritis, especially the early rheumatoid type, no matter how expertly done diathermy or ion transfer applied once or twice a week in a physician's office is not as effective as mild heat treatment applied daily or several times a day followed by gentle massage and suitable exercise. Heat lamps, paraffin packs, whirlpool baths may be all employed in the home, members of the family may be instructed in a simple massage routine and in putting joints through the fullest possible range and in carrying on suitable walking and postural exercises, provided that there is continuity of active medical supervision and interval treatment at the office. Portable diathermy and other electrical apparatus have no place for self treatment at home, for laymen make the most unpredictable blunders in applying such devices, as shown by some tragic happenings, at their best, in most cases these home diathermy machines serve only as glorified heating pads paid for at an excessive price. Intelligently supervised home use of simple physical measures based on proper diagnosis and forming part of a broad therapeutic plan, should play an important role in the modern management of many cases of chronic arthritis.

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WHAT CAN ORTHOPEDICS OFFER THE ARTHRITIC?

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THE orthopedic surgeon can offer the arthritic much in the way of prevention and correction of deformity

GENERAL PRINCIPLES OF ORTHOPEDIC CARE

1. Prevention of deformity by
 - (a) Rest.
 - (b) Physiotherapy (heat, massage active and passive exercises)
 - (c) External support.
 - (d) Manipulative therapy
2. Correction of deformity by
 - (a) Manipulative measures
 - (b) Surgery
3. Improvement of joint function by
 - (a) Conservative measures—physiotherapy
 - (b) Radical measures—arthroplasty osteotomy
4. Alleviation of pain by
 - (a) Splintage.
 - (b) Physical and x ray therapy
 - (c) Surgery—arthrodesis of involved joints

GENERAL REMARKS CONCERNING ORTHOPEDIC CARE

An important phase in the therapy of the arthritic is early orthopedic planning, for the main aim of the orthopedist is to preserve the function of the joint or to restore such function when impaired.

It has long been recognized that one of the important principles in the treatment of the arthritic is that of resting the affected joint. There is less danger of the formation of ankylosis, adhesions or the loss of motion if such joints are rested by splinting than if they are continuously moved. Ankylosis does not develop when a joint is temporarily immobilized, it is usually the result of an inflammatory process resulting in destruction of the articular cartilage.

One of the commonest fears of the arthritic is that of pain resulting from motion of the irritated joint. This in turn gives rise to muscle spasm and is one of the causes of flexion deformity.

Muscle spasm is an early sign of joint irritation and indicates the necessity for rest and not motion. An excellent means of overcoming the fear complex is to resort to underwater exercises, then splint the joint during sleeping hours to relieve pain and prevent deformity.

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Poor Posture—Poor posture is a constant source of discomfort and in the arthritic it is a cause of pain. The characteristic postural defects are those of round shoulders, prominent abdomen, knock knees and pronated feet.

Those who assume the care of the arthritic must constantly stress the need for improvement of the mechanics of the patient by improvement of the general posture. The correction of poor posture in the arthritic should be begun as soon as possible even though the patient is bedridden.

PREVENTION OF JOINT DEFORMITY

Deformity of Shoulder.—An arthritic shoulder tends to become adducted and internally rotated. As a result of disuse the abductors become atrophied and the joint motion is interfered with. Pain radiates

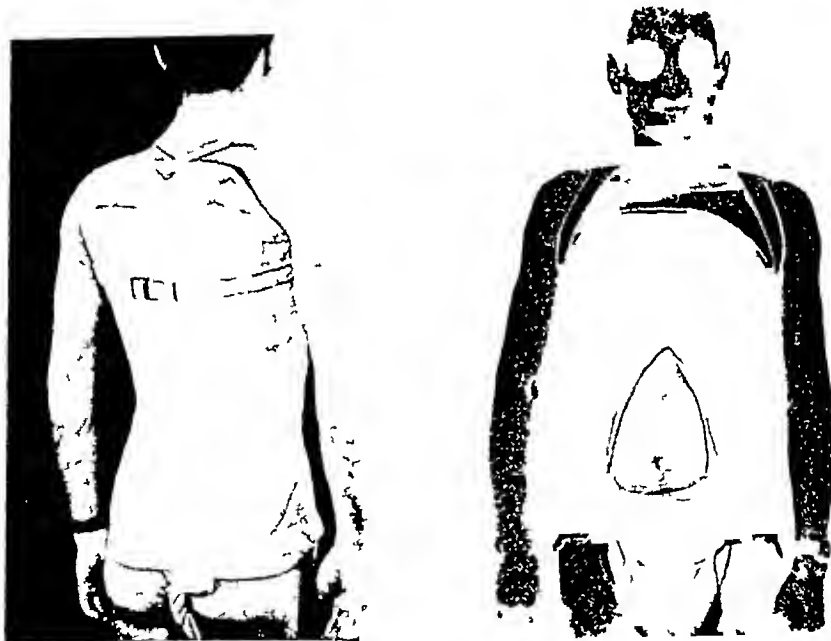


Fig 97—A well-fitting plaster jacket used in disturbances of the spine

from the shoulder down along the lateral aspect of the arm and occasionally towards the fingers. The patient usually points to midway between the shoulder and elbow as the site of pain.

The adduction deformity can be prevented by placing pillows or sandbags in a position to maintain the arm in abduction. By means of a simple overhead device the patient can be encouraged to exercise the arm when recumbent.

Acute pain can be materially lessened by the use of intermediate x-ray therapy subsequently followed by physical therapy such as mild

heat, massage active and passive exercises Neither heat nor cold should be applied to the area treated by the x ray therapy for two to three weeks following the therapy

Deformity of the Spine.—Deformity of the spine can be prevented by maintaining the patient flat on a firm bed, this is accomplished by placing a board between the mattress and spring The use of pillows is discouraged except for short periods during the day At meal

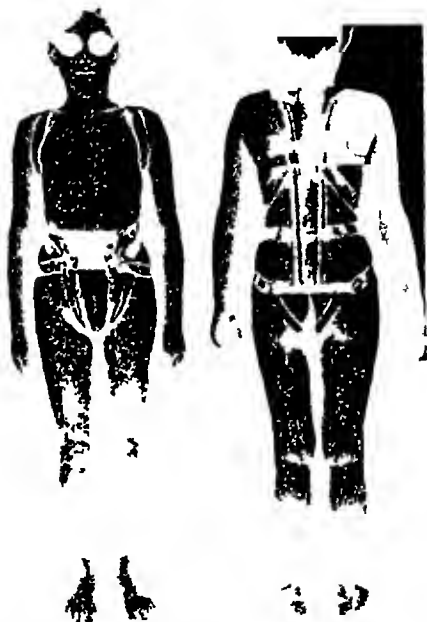


Fig. 98—An excellent brace for maintaining proper posture It can also be used in the early arthritic spine for the relief of pain and for improvement of posture

times the patient is propped up with a triangular mattress or hinged board and the proper torso posture is maintained.

In extremely painful spinal arthritis the torso may be supported by means of a plaster bed This bed is easily made by molding plaster bandages to the patients torso when prone. When dry the plaster is removed, padded and the rough edges are trimmed

When ambulatory the patient is fitted with a Knight spinal or similar type of brace (Fig. 98)

Corrective exercises are begun when the patient is recumbent in order to maintain good muscle tone

Deformity of the Hip.—The deformity common to the hip in the arthritic is one of flexion, adduction and internal rotation. In acute cases this deformity can be prevented by the application of a plaster spica which is subsequently bivalved so that the part may be treated.

In the less acute stage Russell traction (Fig 100) has proven itself to be most satisfactory for the relief of muscle spasm and deformity. The traction is so arranged that it is easily removed for the purpose

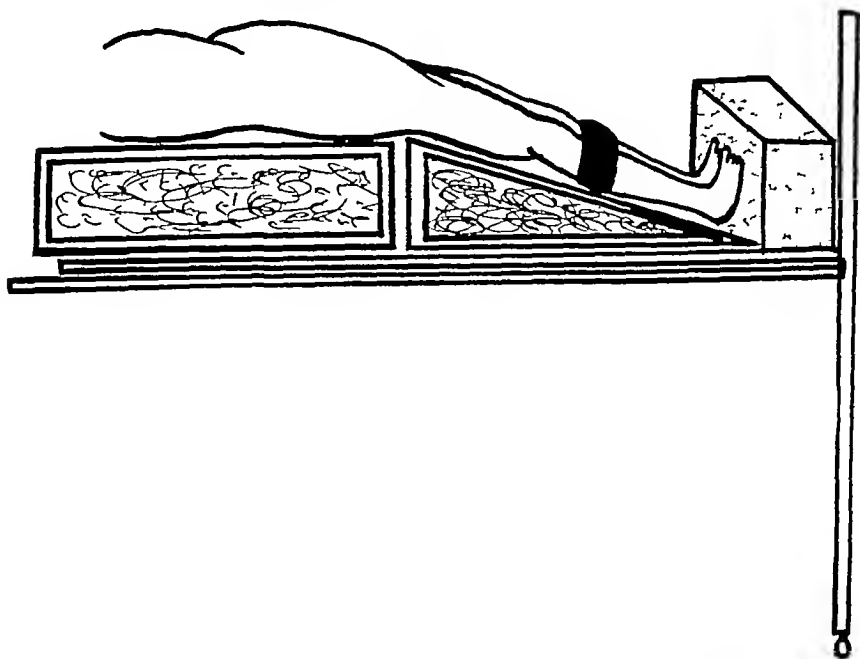


Fig 99—This depicts a triangular mattress with a box placed at the foot of the bed, and sand bags across the lower extremities immediately below the knees holding the limbs in position. The object of this procedure is to assist in preventing or correcting a flexion deformity of the hips.

of physiotherapy. If a canvas anklet is not available one may use a shoe with straps attached to either side of the shoe, and the wooden stirrup is fastened to the straps with the pulleys attached to the stirrup.

When the patient is ambulatory a canvas or leather hip spica, a Thomas splint or a spica made from 6 inch commercial elastic bandages reinforced with starch bandages may be used for temporary immobilization.

Deformity of the Knee.—This is one of the common and disabling deformities occurring in the arthritic patient. It is most often caused by placing pillows beneath the knees for relief of pain. It should therefore be a rule never to place a pillow beneath a knee except on certain specified occasions and then for only short periods of time.

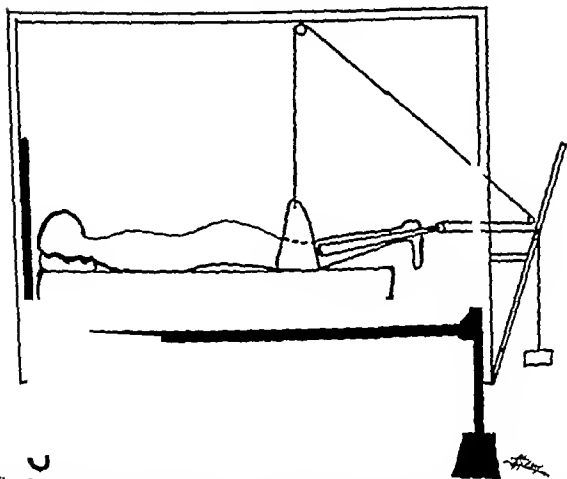


Fig. 100.—Russell traction with the patient in the prone position. A sling is placed above the level of the knee for correction of deformity of knee or hip. With this apparatus the patient need not be constantly kept in one position, for the traction allows him to lie in either the supine or prone attitudes.

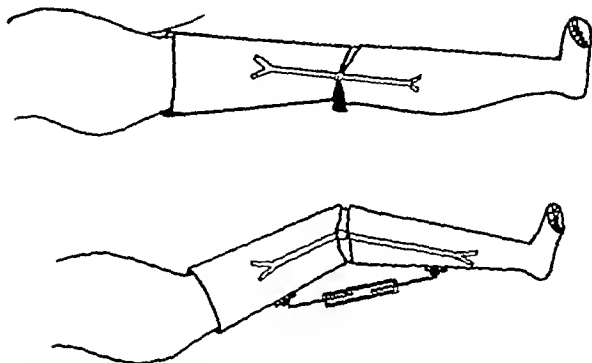


Fig. 101.—The upper drawing shows a lower extremity encased in plaster in which is incorporated hinged metal side bars. The plaster is split and wedged posteriorly for the purpose of correcting a flexion deformity. The lower drawing represents a similar apparatus but instead of using wedges for correction of deformity a turnbuckle is incorporated.

Bed rest may be obligatory during the acute stage while the knee is swollen. At such times long posterior molded plaster splints are applied, the splints may be removed for treatment. Following heat applications the knee joints are passively and painlessly moved by the physician or trained technician. The patient is taught quadriceps exercises in order to maintain good muscle tone.

In the subacute or chronic case the use of molded plaster splints during sleeping hours is recommended for several months. Russell traction is an excellent means of preventing both flexion and subluxa-

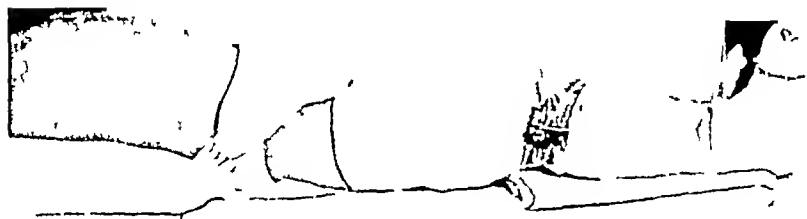


Fig 102 —This is another means of correcting a flexion deformity of the knee. The lower extremity is encased in plaster in which is incorporated two metal hinged side-bars. A long section of wood is incorporated in the proximal portion of the plaster and by means of a rope and windlass arrangement the flexion deformity is corrected.

tion of the knee, the deformities frequently found in atrophic arthritic joints. The Russell traction can be used with the patient in either the supine position or the prone position. When the patient is supine the sling is placed beneath the calf and when prone the sling is placed under the thigh. The patient should not be allowed out of bed until he can fully extend the knee and maintain the extremity in the horizontal position while sitting.

Deformity of the Ankle and Foot —Deformity of the ankle and foot is common in the arthritic and results in hammer toes, lateral deviation of the toes, hallux valgus, thickened painful metatarsophalangeal joints, pronated feet and peroneal spasm. These deformi-

ties can be prevented by the use of physical therapeutic measures and the application of posterior molded splints. The molded splints should extend beyond the limits of the toes. A cradle is used to avoid pressure of bed clothing on the toes, eliminating both pain and deformity. When the patient is ambulatory deformity can be improved by the use of various shoe wedges, leather or rubber molded arch supports, and strappings.

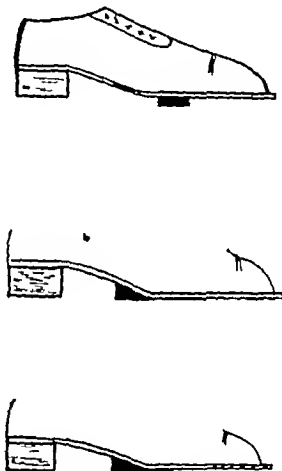


Fig. 103.—The top drawing represents the use of a metatarsal bar. The middle drawing is that of an anterior heel and the bottom one represents the combination of the two. These appliances are indicated in painful metatarsophalangeal joint arthritis.

Where the deformity is complicated by peroneal spasm the spasm can be overcome by injection of novocaine into the peroneal muscles or the use of ethyl chloride spray over the common peroneal nerve as it courses over the head of the fibula. Following either of these procedures the foot is immediately strapped in inversion.

In long standing cases gentle manipulation under intravenous anesthesia followed by the application of a skin tight walking plaster is the procedure of choice.

MANIPULATIVE THERAPY

Manipulation therapy is used for the purpose of increasing the range of motion of a joint where motion is limited because of the presence of adhesions which have been allowed to form as a result of

either unnecessary immobilization or early active excessive mobilization. Early excessive mobilization results in adhesions because of increasing damage to the joint during the early stage of the disease. Manipulative therapy may also be resorted to when flexion contractures have resulted.

Manipulation of the joint is successful when there is no longer any active process within the joint and when the limitation of motion is due primarily to adhesions or contractures.

Manipulation of the joint for the breaking up of adhesions should be performed with the patient under complete narcosis. With the use of intravenous anesthesia a joint can be gently and repeatedly manipulated, and when the patient is completely relaxed it is found that very little force is required. Much harm is done by the injudicious use of force during manipulation for the joint may become stiffer than it was before. If the adhesions are not readily broken up one must immobilize the joint in plaster, rest the part for several days, then undertake a second and even a third manipulation. The patient recovers quickly from the effects of an intravenous anesthetic and is encouraged to exercise the limb immediately.

Gentle manipulation followed by immobilization, repeated on several occasions, will aid in the correction of contractures.

ORTHOPEDIC SURGERY IN ARTHRITIS

Osgood has stressed certain factors which must obtain before surgery is considered. These are in their order of importance (1) quiescence of the arthritic process for several months prior to surgery, (2) optimum general condition of the patient, (3) good morale on the part of the patient, and (4) adequate facilities for hospital and follow-up care.

It is good practice to teach the patient exercise of the involved joint for several weeks prior to surgery in order that he may be better able to cooperate during convalescence.

Synovectomy.—This is a procedure wherein the lining of a joint is excised, it is applicable only in the knee.

Synovectomy of the knee is indicated in some chronic cases in which the synovial lining of the pouch is thickened and villous in type and the fat pads are enlarged. It is also indicated in persistent hydrops of the knee which is resistant to other forms of therapy. In the performance of a synovectomy in a chronic arthritic knee the patella should be thoroughly inspected and if found to be fibrillated it should be removed.

In rheumatoid arthritis synovectomy should be used in those cases in which there is little or no involvement of the cartilage or bone and the sedimentation rate has been known to be normal for at least six months. In contemplating synovectomy in rheumatoid arthritis it is

good practice to subject the joint to active physiotherapy, check the patient's temperature daily and check the sedimentation rate on one or more occasions in order to determine whether a flare-up of the infection ensues. If such is the case the synovectomy should be postponed.

Synovectomy is contraindicated in a tuberculous synovitis of the knee. There are many instances of chronic synovitis without bone disease or cartilage destruction that present the appearance of a chronic nontuberculous arthritis. When operated upon these joints may present the pathological picture of a chronic nontuberculous arthritis on macroscopic examination, yet on microscopic sectioning tubercles are found. The end result in such cases is invariably poor and the joint undergoes rapid destruction.

This can be guarded against if prior to surgery the joint is aspirated for guinea pig test. If free fluid is not encountered at the time of aspiration several cc. of sterile water may be injected and reaspirated for guinea pig inoculation.

Posterior Capsulotomy—This is an operative procedure used in flexion contractures of the chronic rheumatoid knee where there has been little cartilaginous damage and where the tibia subluxates posteriorly on the femur.

The operation is performed by sectioning the hamstrings, gastrocnemii and the posterior capsule of the knee joint. The hamstrings are then lengthened and resutured.

Arthrotomy—By arthrotomy is meant incision of the joint for the purpose of removing loose bodies or large hypertrophic villus formations.

Osteotomy—This is a procedure wherein the shaft of a bone near a joint is sectioned for the purpose of correcting a deformity and improving the weight bearing mechanics of a deformed part. It is commonly used about the hip for correction of a flexion adduction deformity. It is occasionally used instead of a posterior capsulotomy of the knee and in this instance the lower end of the femur is sectioned and angulated posteriorly.

It is an axiom in orthopedic surgery that correction by osteotomy is preferable to soft tissue sectioning for in the latter, recurrences are apt to take place if the patient cannot be kept under direct orthopedic control for many months following surgery.

Arthroplasty—This is a method of restoring mobility of an ankylosed joint. It is an operation in which an artificial joint is modeled to imitate a destroyed previously existing one. The operation has been successfully used in the temporomandibular, hip and knee joints. It is not justifiable where there has been involvement of the shoulder, wrist or ankle joints. The most suitable age period for an arthroplasty is between 20 and 45 years. The operation is contraindicated in tuberculous lesions.

Where an arthritic exhibits an ankylosis of both knees only one may be operated upon at one time When both hips are ankylosed only one hip is operated upon at one time When both hips and both knees are involved then one hip and the opposite knee are subjected to surgery There are instances where both hip or knee joints may be operated upon for the purpose of remodeling a new joint. The interval between such operations should be two or more years and should be one of election on the part of the patient

Arthrodesis—This is an artificial means of creating ankylosis During the process the joint space is obliterated and the raw bony surfaces approximated to establish bony continuity

There are instances in which arthrodesis can be performed without destroying the joint, this is known as an extra-articular arthrodesis and is used in the shoulder, elbow and hip joints

Arthrodesis is useful in monarticular arthritis where it is advisable to produce a painless stiff joint, especially in weight-bearing joints where stability is essential It is ill-advised in rheumatoid arthritis, for ankylosis frequently results without surgery There, however, are instances in which surgery is advisable as in arthritis of the feet with destruction of the tarsal and subtalar joints These joints are quite painful and interfere with the mechanics of the extremities, hindering recovery

Excision of the Patella.—During recent years excision of the patella has been used with increasing frequency It is a useful operation in a small selected group of patients who are afflicted with either rheumatoid or degenerative arthritis of the knee Excision of the patella eliminates a mechanical impediment to the function of the knee and allows of freer motion with considerable lessening of pain

SUMMARY

The writer has attempted to outline the orthopedic care for the prevention and correction of the various deformities which may occur in the chronic arthritic

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CHOLESTEROL CONTENT OF URINE IN ARTHRITIS

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A BRIGHT chapter in organic chemistry was written by the workers who identified the structural characteristics of the sterols. By 1933 Rosenheim and King, Windans, Bittenandt and others¹ were convinced that the phenanthrenecyclopentane structure known as the cholane nucleus was the characteristic grouping of the sterols. This made possible the statement of the formula for cholesterol.

Cholesterol is an essential constituent of all cells and body fluids. It exists in a free state, and as esters when combined with fatty acids in the blood. The brain, suprarenals and malignant tumors have the richest supply of cholesterol. It is necessary for life and if not supplied in adequate amounts it may be synthesized, but the mechanics of this is unknown. Our knowledge of the functions of cholesterol is largely based on circumstantial evidence, and is often theoretical. Although the marked variations for cholesterol in health and in disease are well known, they must be interpreted with caution.^{2, 3, 4}

The relation of blood cholesterol to arthritis was investigated by Hartung and Bruger.⁵ They found that the cholesterol content of the plasma was increased in osteoarthritis and was decreased in rheumatoid arthritis. There are no reported studies of the cholesterol content of the urine from patients with arthritis.

The present investigation presents such a study with an analysis of the possible relationship between urinary cholesterol, plasma cholesterol, and the erythrocyte sedimentation rate in thirty cases of definite arthritis.

METHOD

Twenty-four hour specimens of urine from these patients were analyzed according to the procedure developed by Bruger and Ehrlich.⁶ A routine analysis was done on each specimen and if any abnormality was found the specimen was not accepted.

One hundred cubic centimeters of urine were placed in a 150 cc beaker. The urine was acidified with 0.5 cc of concentrated sulfuric acid, and 10 cc of diluted egg albumen solution was added. After mixing, the albumen was precipitated by the addition of 5 cc. of 10 per cent solution of sodium tungstate. The contents were again well mixed,

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and the precipitate was allowed to settle out for five to ten minutes. The solution was filtered through a fluted filter paper (previously rendered fat free by washing in alcohol and ether). The protein precipitate was washed repeatedly with hot distilled water, the extent of the washing varied with the quantity of urinary pigment in the protein coagulum (50 cc to 100 cc of water usually sufficed). The precipitate and filter paper were transferred to a 150 cc beaker, and 30 cc. of a 3:1 alcohol-ether mixture were added. This was allowed to stand for fifteen to thirty minutes. The beaker was then placed on an electric hot plate. The contents were brought to the boiling point after which they were filtered through fat-free paper into another beaker. Two additional extractions with alcohol-ether were made, and the filtrates were combined. The alcohol-ether extract was placed in an incubator (37° F) and evaporated to dryness. To the dry residue in the beaker, 30 cc of petroleum ether (B.P. 30° to 50° C) were added. The beaker was then placed on a hot plate and the petroleum ether was evaporated to approximately 10 cc. volume. This was filtered through fat-free cotton or filter paper into another beaker, two additional petroleum ether extractions were carried out, and the extracts were combined. This extract was placed in an incubator (37° C) and was evaporated to dryness. The residue was extracted with 5 cc of chloroform.

The chloroform extract was transferred to a graduated cylinder of 10 cc. capacity, 2 cc of acetic anhydride and 0.1 cc of concentrated sulfuric acid were added. A standard solution containing 0.5 mg of cholesterol in 5 cc of chloroform was prepared simultaneously for the development of the Liebermann-Burchard color reaction. A red filter (Wratten 71-A) was used to facilitate color matching.

$$\text{Calculation } \frac{R_s}{R_u} \times 0.5 \times \frac{100}{x} = \text{mg cholesterol in 100 cc. of urine}$$

R_s = reading of standard

R_u = reading of unknown

x = volume of urine extracted

For the determination of cholesterol in normal urine approximately 300 cc of urine must be extracted if the twenty-four-hour urine volume does not exceed 1500 cc. With dilute urines, larger amounts must be extracted. This is done, preferably, by working with 100 cc quantities and combining the petroleum ether extracts.

Venous blood was obtained on the same day that the urine was collected, to ascertain the plasma cholesterol content (modified Bloor procedure⁷) and the sedimentation rate (Westergren).

The total cholesterol output was calculated by multiplying the urine volume in twenty-four hours by the urinary cholesterol per 100 cc.

RESULTS

Table 1 shows the results in twelve cases of rheumatoid arthritis under treatment, the patients ranging in age from 35 to 61 years. The

duration of the disease varied from one to twenty seven years. The highest urinary cholesterol was 2.54 mg., and the lowest was 0.66 mg in twenty four hours. In patients numbered 4 and 11, the plasma

TABLE 1.—CHOLESTEROL CONTENT OF URINE IN PATIENTS WITH RHEUMATOID ARTHRITIS

Patient	Age	Sex	Duration	Sed. Rate, mm./hr	Plasma Cholesterol mg /100 cc.	Urine Cholesterol mg /24 hr
1	35	F	10 years	49	150	2.54
2	40	F	6 years	30	195	0.11
3	31	M	1 year	8	275	0.66
4	55	F	15 years	25	450	2.3
5	61	F	4 years	62	150	1.12
6	37	F	1 year	46	180	0.72
7	36	F	2 years	33	165	1.42
8	44	M	3 years	7	170	1.25
9	51	F	4 years	64	215	0.97
10	57	F	27 years	10	205	1.12
11	35	F	10 years	77	465	1.48
12	42	F	5 years	65	210	1.7

TABLE 2.—CHOLESTEROL CONTENT OF URINE IN PATIENTS WITH OSTEO-ARTHRITIS

Patient	Age	Sex	Duration	Sed Rate mm./hr	Plasma Cholesterol, mg /100 cc.	Urine Cholesterol, mg /24 hr
1	65	F	10 years	26	210	2.23
2	57	M	1 year	38	205	0.97
3	47	F	10 years	3	320	1.72
4	35	M	3 years	16	230	0.89
5	47	F	8 years	33	210	1.39
6	52	F	27 years	21	230	1.47
7	65	F	35 years	29	230	4.0
8	61	F	3 years	11	260	1.14
9	53	F	5 years	15	165	2.33
10	54	F	5 years	39	285	0.97
11	63	F	20 years	33	170	2.55
12	49	F	2 years	28	255	3.1
13	65	F	12 years	38	210	0.68
14	56	F	12 years	24	195	2.83
15	55	F	4 years	13	260	1.0
16	55	F	6 years	25	190	2.46
17	57	F	3 years	28	205	3.4
18	64	F	10 years	8	215	0.88

cholesterols were respectively 450 and 465 mg. per 100 cc. and the urinary cholesterols 2.3 and 1.48 mg in twenty four hours. For all patients, the excretion of cholesterol varied from 0.14 to 2.54 mg. in twenty four hours.

Table 2 shows the excretion of cholesterol in eighteen cases of osteoarthritis, which ranged from 0.68 to 4 mg in twenty-four hours. The ages of the patients ranged from 35 to 65 years.

There was no correlation between the sedimentation rate, plasma cholesterol and the cholesterol content of the urine.

Despite the fluctuating values in the plasma cholesterol, the excretion of the urinary cholesterol remained within normal limits for all patients.

CONCLUSIONS

1. In twelve cases of rheumatoid arthritis and eighteen cases of osteoarthritis there was no relationship between the plasma cholesterol level, sedimentation rate and the urinary cholesterol.

2. The urinary cholesterol excretion was within normal limits in all cases.

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CLINICS ON OTHER SUBJECTS

THE TREATMENT OF SYPHILIS WITH PENICILLIN

GEORGE X. SCHWEMLEIN, M D *

THE recent introduction of penicillin into the therapeutic armamentarium of syphilis promises to greatly facilitate the treatment and control of the disease. Extensive investigations under government sponsorship, concerning the efficacy of the drug in the various stages of syphilis are under way in numerous clinics and research centers. While the results of these studies are not conclusive, there have been several preliminary reports and it is the purpose of this presentation to summarize briefly the available knowledge.¹

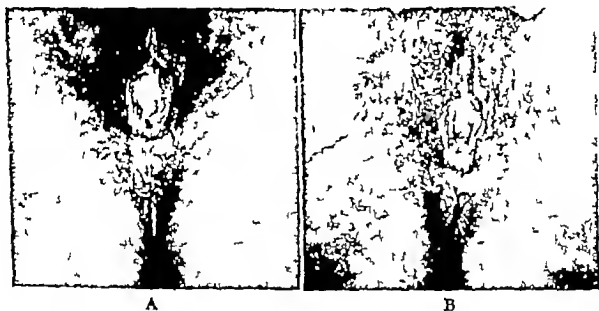


Fig 104—A, Primary syphilis. Hypertrophic chancre on perineum. B After four days of penicillin therapy. Beginning involution of lesion.

Primary and Secondary Syphilis—Penicillin has in the main, been administered on a plan requiring sixty intramuscular injections over seven and one-half days, the dosage interval being three hours. Studies concerning the combination of penicillin with other drugs such as the arsenicals and/or bismuth, or adjuvantive therapy with fever are also

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being carried out. The problem has been to determine the total dosage of penicillin required. The first effort in this direction was to study the comparative effectiveness of four treatment groups within the twenty-fold range of 60,000 to 1,200,000 units.

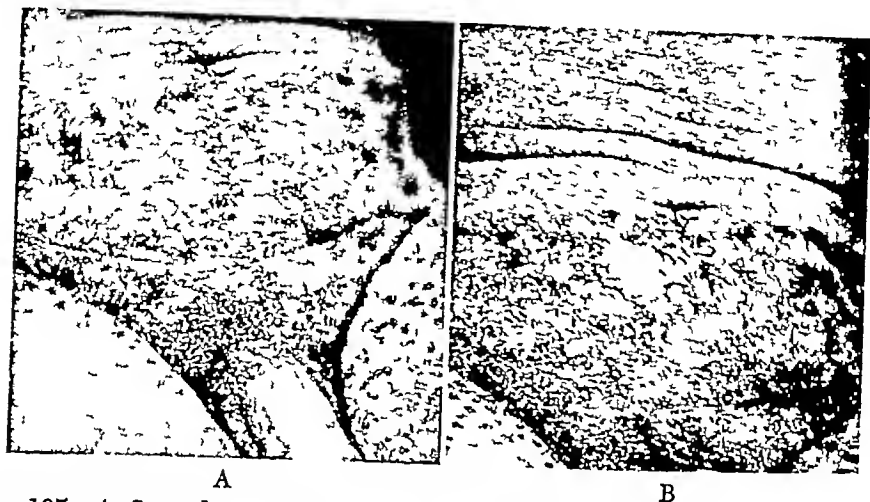


Fig 105—A, Secondary syphilis. Generalized psoriasisiform eruption. B, After four days of penicillin therapy. Desquamation and beginning involution of lesions.

Penicillin, regardless of dosage, has a profound immediate effect on early syphilis in terms of disappearance of treponemes from skin lesions, with prompt healing of the lesions (Figs 104 to 109) and a

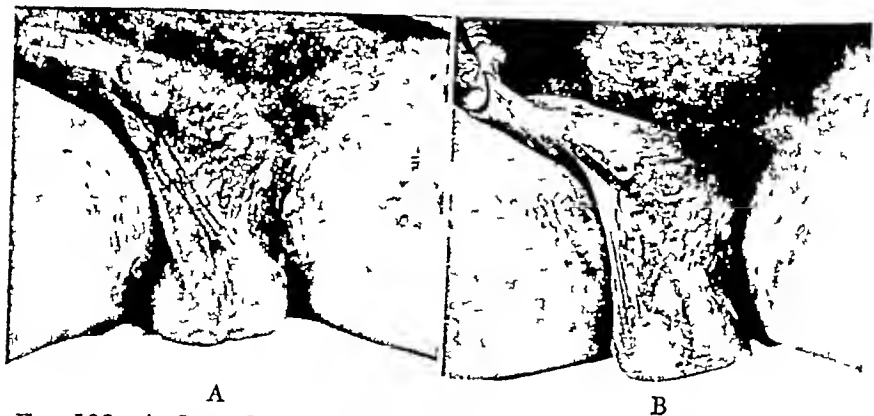


Fig 106—A, Secondary syphilis. Eroded papules of genitalia. B, After four days of penicillin therapy. Peripheral epithelization of the lesions with marked subsidence of nonspecific infection.

tendency toward reversal of the blood serologic tests (Fig 110). As there were the same immediate therapeutic effects regardless of total dosage, it was obvious that these factors could not be used to determine the effectiveness of a given treatment schedule.

The factor which so far has proved of importance is the comparative incidence of relapse, both clinical and serologic. The relapse rates



A

B

Fig 107—A, Secondary syphilis. Eroded papules about preputial orifice and acute balanoposthitis. B After four days of penicillin therapy. Epithelialization of the papules and subsidence of the acute balanoposthitis.



A

B

Fig 108—A, Secondary syphilis. Annular lesions of the face. B After four days of penicillin therapy. Subsidence of peripheral infiltration with remaining hyperpigmented central areas of the lesions.

have been as follows: 60 000 unit total dosage—100 per cent, 300 000 unit—75 per cent, 600 000 unit—40 per cent, and 8–20 per cent in the

1,200,000 unit total dosage group These figures are based on a small number of cases and eventually, after a longer period of observation,



Fig 109—A, Secondary syphilis Condylomata lata of the vulva B, After four days of penicillin therapy Involution of the lesions

may be considerably higher in each group For the present, it is evident that the relapse rate is in an inverse ratio to the total dosage, i e, the lower the total dosage the higher the incidence of relapse

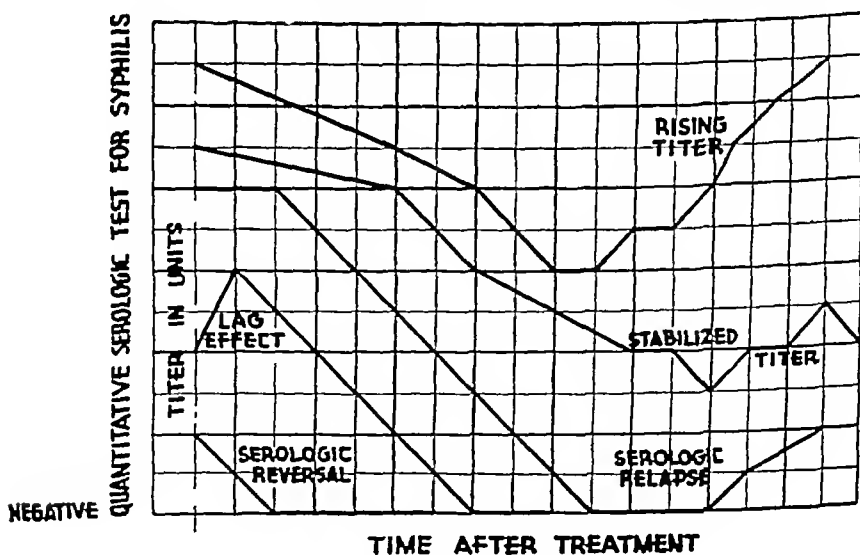


Fig 110—The various types of serologic response which occur after penicillin therapy of early syphilis The broken vertical line indicates the termination of penicillin treatment The heavy vertical lines indicate time in month periods The unit expression of the quantitative titer varies with the method of serologic testing

A group of patients observed eighteen months after receiving 300,000 units of penicillin, i e, 5000 units, intramuscularly, every three

hours for eight days (sixty injections) and 0.04 gm of mapharsen daily for eight injections, concomitantly, reveal that this method is unsatisfactory although, as may be expected, more successful than this amount of penicillin alone. It is entirely possible that a larger total dosage of penicillin employed with mapharsen may yield a better curative rate than when either drug is used alone.

Penicillin holds the inestimable advantage over other forms of treatment in freedom from serious risks of chemotherapy. A mild Herxheimer reaction, however, occurs in some of the patients. When evident, it appears usually during the first forty-eight hours, consisting of fever, chills, general malaise and occasionally intense pain at the sites of genital lesions. It usually does not require termination of the treatment and is only transient in character. Other reactions consist of menstrual disturbances, urticaria, itching and other allergic skin conditions.²⁻⁵

Early Syphilis Masked by Penicillin Treatment of Gonorrhea—Care must be exercised in treating gonococcal infections with small amounts of penicillin (50,000–150,000 units), for concomitant undiagnosed primary syphilitic lesions may heal entirely only to recur; secondary lesions may develop or the patient may unrecognizedly progress to the late sequelae of the disease. Even should the syphilitic lesions be discovered before healing occurs, they are rendered extremely difficult for diagnosis because of the rapid destruction of the surface treponemes by the inadequate doses of penicillin.

It is, therefore, of great importance to make certain that a patient with gonorrhea is not also developing primary or secondary syphilis before administering small amounts of penicillin for gonorrhea.⁷⁻¹⁷

Treatment Resistant Early Syphilis.—Psoriasisform lesions of early syphilis which are resistant to the arsenicals and bismuth heal favorably with penicillin. Varying dosage schedules have been employed ranging from a total dose of 60,000 to 2,000,000 units, although the dosage recommended is 2,400,000 units intramuscularly, every three to four hours, day and night for sixty injections.^{18, 19}

Early Syphilis and Pregnancy.—Pregnant women in the various trimesters manifesting darkfield positive primary or secondary syphilis have been administered penicillin. The time-dose relationship has been 20,000 units intramuscularly, every three hours for fifteen days (1,200,000 units total). There have been prompt healing of the lesions and a favorable influence on the serologic tests with no interference to the pregnancy. Much time is required to determine the incidence of congenital syphilis although there is no immediate indication that the rate will be unfavorable.

The action of penicillin in stimulating uterine contraction and bleeding in pregnant women has been the subject of a recent report. Symptoms of uterine activity as cramps and bleeding threatened abortion, and actual abortion were observed.

The effect of penicillin on *menstruation* is well known. In some cases, patients who have a history of delayed menstruation promptly begin to bleed soon after the administration of the drug. Other patients bleed for longer periods than normal with a more profuse flow than usual. Others complain of intermenstrual bleeding as soon as penicillin is administered.

Whether these phenomena are due to "a form of therapeutic paradox (Herxheimer reaction)," impurities in the penicillin or an oxytocic action similar to that of ergot is not yet clear. As the oxytocic action of ergot, a biological product of another mold (*claviceps purpurea*), is well understood, it is entirely possible that the mold *Penicillium notatum* may have similar activity, but much weaker in intensity.²⁰⁻²²

Reinfections—The problem of reinfection is assuming much more practical importance than it had before the advent of intensive arsenical and penicillin therapy in syphilis. Using more liberal criteria, reinfections are from five to ten times as common after these rapid forms of therapy than after the long-term systems of therapy.

The very descriptive term "ping-pong syphilis" is being adopted to describe the condition which occurs when one sexual partner reinfects the other who has recently received intensive treatment. Under such conditions, one partner continually harbors the infection, while the other is receiving therapy so that it is a public health necessity that sexual partners be thoroughly examined and treated if necessary before the penicillin-treated patient is dismissed from the hospital.²³

Infantile Congenital Syphilis.—Preliminary investigations in infants with early manifest syphilis treated with penicillin show gratifying results. The total dosage schedules employed are 40,000 to 80,000 units per kilogram of body weight, administered as sixty intramuscular injections over a seven and one-half day period. Cutaneous and mucous membrane lesions heal during or shortly after treatment, rhinitis, having been somewhat more persistent, healing in from two weeks to two months. Roentgenographic evidence of osteitis disappeared in two to six months. Regression of hepatic, splenic and lymph node enlargement, though variable, is usually completed in three months. There have been three reported deaths during or soon after treatment but whether the deaths were directly or indirectly due to penicillin or syphilis is not known.²⁴⁻²⁵

Latent Syphilis.—As the problem of penicillin treatment of latent syphilis has been relegated to the future, there is little clinical experience to offer the practitioner with the patient exhibiting a positive blood test and no other laboratory or clinical evidences of syphilis.

Cardiovascular Syphilis.—There is the possibility that penicillin may be too intensive an agent in the therapy of cardiovascular syphilis as evidenced by the report of the development in two patients of clinical manifestations of coronary artery insufficiency while receiving the drug. Both patients had received preliminary therapy with bis-

Spinal fluid examinations revealed an immediate response of an elevation in cells and total protein in most of the previously untreated patients, followed by a general gradual reduction in cell count, total protein and, later, a decrease in the Wassermann titer. Comparison between the clinical and serologic results show no definite correlation at the present.

It is possible that the inclusion of fever therapy in addition to penicillin in this clinical investigation enhances the good clinical results, although the great majority of patients received the fever therapy in approximately one-half the amount generally accepted as sufficient.

Electroencephalograms of patients suffering from neurosyphilis were studied before and after penicillin therapy (4,000,000 units within ten days). Many formerly abnormal electroencephalograms became normal and most of the remaining records showed varying degrees of improvement. The abnormal electroencephalograms were interpreted as the consequence of local cerebral anoxia and of generalized or localized cerebral inflammation. Many of the abnormalities are apparently reversible. These findings indicate that the electroencephalograms can often be used as a valuable adjunct in determining the effect of penicillin treatment in central nervous system syphilis.

The immediate favorable clinical results when penicillin is used in *syphilitic meningitis* are noteworthy, both from the laboratory and clinical standpoint. The total amount of penicillin used varied from 600,000 to 4,000,000 units administered every three to four hours, day and night, for from eight to sixteen days.

The intracisternal and intrathecal administration of penicillin has been reported with favorable clinical response, although severe reactions have occurred from apparent overdosage. From the data presented, it is apparent that penicillin is an active and effective therapeutic agent for neurosyphilis. Caution is advised in the interpretation of these results and it is believed that the time has not arrived for the distribution of penicillin for general use in the treatment of neurosyphilis.³⁰⁻³⁷

SUMMARY

For the present, it may be concluded that penicillin is an effective addition to the methods used in the treatment of syphilis. The proper time-dose relationships, are, as yet, not established, but are under well-organized, large-scale, governmentally-sponsored study from which satisfactory treatment schemes may be expected eventually to emerge.

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HYPERTENSION DUE TO ARTERIOSCLEROSIS, AND ITS COMPLICATIONS

I. W. HELD, M.D., F.A.C.P.*

At the outset, let us state that we agree with most authors that hypertension in itself is not a disease. It is a leading symptom, just as elevation of temperature is a symptom, that greatly influences the course and outcome of some underlying affection.

What that affection is cannot always be determined and to the hypertension of unknown origin Allbutt¹ applied the name *hyperpiesia*. This has been changed by popular usage to "essential hypertension," and the present trend is to regard all cases as of either essential (unknown) origin, and which may be either benign or malignant in nature, or due to renal disease. In the course of that disease a certain pressor substance is liberated and causes the symptom of hypertension—this is the theory of Goldblatt and his co-workers.²

Actually, however, there are many determinable causes of hypertension. One has only to recall patients whose increased cardiac output alone is responsible for hypertension to realize this. A physician who properly prescribes therapy and correctly evaluates prognosis will delve into all possible causes in order to establish the correct one. As an aid to diagnosis, we offered a classification a few years ago³ that was based on etiology. Because this has lost none of its usefulness in the interim though sometimes it seems to have been forgotten we venture to repeat it here.

CLASSIFICATION OF HYPERTENSION ON THE BASIS OF ETIOLOGY

- I Vascular Hypertension
 - 1 Functional (psychogenic)
 - 2 Organic arterial due to:
 - (a) Arteriosclerosis
 - (b) Coarctation of the aorta
 - (c) Arteriovenous aneurysm
 - (d) Aortic regurgitation
 - (e) Acrodynia
- II Hypertension due to Endocrine Dysfunction
 - (a) Gonadal
 - (b) Thyroid
 - (c) Pituitary
 - (d) Adrenal

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III Renal Hypertension, due to

- (a) Glomerular nephritis (secondary contracted kidney)
- (b) Primary contracted kidney
- (c) Amyloid kidney
- (d) Polycystic kidney
- (e) Surgical disease of the kidney
 - (1) Pyelonephritic contracted kidney
 - (2) Primary contracted kidney
 - (3) Hydronephrotic kidney
 - (4) Ectopic kidney
 - (5) Amyloid contracted kidney
- (f) Periarteritis nodosa

IV Hypertension during Pregnancy

V Essential Hypertension

- (a) Benign
- (b) Malignant

In 1945, Page and Corcoran⁴ offered a similar classification but greatly amplified the group of endocrine disturbances that may cause hypertension. Their classification of these was as follows:

ENDOCRINE DISTURBANCES CAUSING HYPERTENSION

Pheochromocytoma	Pituitary basophilism
Adrenal carcinoma	Acromegaly
Adrenal hyperplasia	Thymic carcinoma
Chorionepithelioma	Hyperthyroidism
Adrenal-like ovarian tumor	Arrhenoblastoma
Cushing's syndrome	

Obviously, it is not our purpose here to discuss all forms of hypertension. Instead, we shall dwell only upon hypertension and its complications occurring during the course of arteriosclerosis, which is one of the most common causes of hypertension.

Not all patients with arteriosclerosis are hypertensive, and hypertension often exists without arteriosclerosis. However, when the two conditions coexist, the immediate signs and symptoms are so characteristic as to merit early diagnosis and suitable therapy.

THE NATURE OF ARTERIOSCLEROSIS

Winternitz, Thomas and La Comte⁵ showed long ago that arteriosclerosis is a constitutional, or aging process, and recently Eli Moschowitz⁶ discussed its pathogenesis so thoroughly that we shall attempt here to point out only a few salient features.

The first manifestation of arteriosclerosis is a hemorrhage in the small nutritive vessels that lie in the walls of the large vessels and which may be recognized as phagocytosed parts in the monocytes (1) as a residue of iron demonstrable with Turnbull's Prussian blue reaction, (2) as grossly yellow linear patches in the aorta, or (3) as large bright red oval masses in parts of the thickened intima where supposedly there are no vessels.

In some cases the hemorrhage first appears in the form of ecchymosis. In certain areas the extravasated blood is replaced at the site of hemorrhage by cholesterol clefts. When this fatty substance extends through the endothelial lining of the lumen it forms an atheromatous ulcer in which fresh blood accumulates not only from the lumen but also from bleeding vessels in the depth of the crater.

Transformation of the fatty, necrotic mass into calcified material results by a mechanism (Klotz) involving saponification of fatty acids to form calcium salts and subsequently calcium phosphate and carbonate. The ultimate concretion is sheathlike or roughly spherical in form. Owing to the fact that no increased resistance is offered to the flow of blood through the peripheral vessels, the sclerotic process results in atheromatous changes, and hypertension need not occur. There may occur, however, aneurysmal dilatation or rupture of a palpebral fissure blocking by atheromatous plaques and other vascular damage.

Should the arteriosclerotic lesion (no matter how minute) develop in any one of the centers regulating blood pressure, hypertension is a direct outcome. These centers are carotid sinus, wall of the aorta, medulla oblongata, midbrain and splanchnic region. The hypertension may be out of all proportion to the degree of sclerosis present in arteries and arterioles elsewhere in the body.

FACTORS PREDISPOSING TO ARTERIOSCLEROSIS

Several factors can predispose an individual to arteriosclerotic changes. For instance, metabolic diseases such as gout and diabetes may do so, or a disturbance in cholesterol metabolism, as pointed out by Amitschkow⁷ and Leary.⁸ Other authors have claimed as a cause an excessive intake of protein but our experience is that this cannot lead to arteriosclerosis unless the individual has an inherent constitutional predilection for the disease.

Another contributory factor is undoubtedly certain occupations, as illustrated by those workers in lead who tend to develop repeated spasm of the vessels followed by arteriosclerosis. Likewise, persons who work under great strain may develop hypertonus of the musculature of the vascular system as a prelude to sclerotic changes in the vascular supply of the organs under greatest stress. This is exemplified by cerebral arteriosclerosis as a result of an unfavorable environmental change or alteration in their habits. We know, for example, that Negroes seldom develop arteriosclerosis so long as they remain in the South but not infrequently do so upon their removal to the North where the competitive struggle for a livelihood is acute and more destructive.

DISTRIBUTION OF SCLEROSIS THROUGH THE ARTERIAL SYSTEM

The most extensive involvement is as a rule of the thoracic aorta, particularly the arch and descending aorta. Next in extent and fre-

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- (a) Glomerular nephritis (secondary contracted kidney)
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DISTRIBUTION OF SCLEROSIS THROUGH THE ARTERIAL SYSTEM

The most extensive involvement is as a rule of the thoracic aorta, particularly the arch and descending aorta. Next in extent and fre-

quency is the abdominal aorta, large renal arteries, and the temporal, radial, popliteal and tibial arteries

Of the small arteries, those most often involved are the cerebral, spinal, coronary, splenic and pancreatic, less often the mesenteric and gastric arteries, and very rarely the arterioles of the kidney

Since the degree of sclerosis is greater in one system than in another, it is not surprising that the symptomatology of arteriosclerosis varies. Some cases are actually asymptomatic. In general, however, symptoms manifest themselves according to the region involved. They may be predominantly thoracic, cerebral, abdominal, renal, tibial or popliteal in nature.

INCIDENCE AND SYMPTOMATOLOGY IN GENERAL

Regardless of the region involved, arteriosclerosis usually makes its appearance when the patient is in his late forties or early fifties. The male is much more often afflicted than is the female. In the male, circulatory disturbances are the more marked, they may be, indeed, the first symptoms to occur. In the female, cerebral symptoms are the more outspoken and are particularly severe during the menopause.

When there is hypertension due to arteriosclerosis, the systolic pressure is usually 100 plus the age of the patient, or slightly higher. In fact, the rule of "one hundred plus the age" for normal systolic pressure is erroneous, it applies only to the patient with hypertension due to arteriosclerosis. This pressure generally drops from 10 to 20 points during sleep but does not go below normal except in patients who have cerebral arteriosclerosis. The diastolic pressure remains at 80 or 90 unless there is sclerosis of the spleen or kidneys.

The foregoing is a point of differentiation between essential hypertension and arteriosclerotic hypertension, that is to say, essential hypertension begins much earlier in life and neither the systolic nor the diastolic blood pressure bears any relation to age but is continuously high, especially the diastolic pressure.

TREATMENT OF VERY EARLY SYMPTOMS

If the arteriosclerotic patient is plethoric, one of his first symptoms may be constipation and a feeling of bloatedness after eating. To alleviate this, his diet should contain 6 to 8 ounces of prune juice morning and night, with increased non-coarse vegetables (spinach, carrots, cauliflower) and he should take no laxative. If this becomes absolutely necessary, then he may have 2 teaspoonfuls of sodium sulfate (Glauber's salt) with 1 teaspoonful of magnesium sulfate (Epsom salt) in half a glassful of cold water upon rising.

Should the patient be asymptomatic questioning may elicit the fact that he tires readily and cannot concentrate as he did formerly. Treatment is largely a matter of preventing fatigue by cessation of activity.

just prior to exhaustion, and psychical excitement must be guarded against. Golfing and other sports are to be carefully controlled.

If the patient is given to indulgence in food, the intake should be so restricted as to reduce weight rather than to risk its increase.

The diet in all cases of arteriosclerosis with hypertension will be discussed in more detail at the end of the paper.

Sedatives like the barbiturate preparations should not be resorted to even in the early stage of arteriosclerosis, except when absolutely necessary to help the patient over an immediate excited state. From the psychotherapeutic standpoint, reassurance is of far greater benefit and is not habit forming.

HYPERTENSION ASSOCIATED WITH ARTERIOSCLEROSIS OF THE THORACIC AORTA

The thoracic aorta can be considerably involved by sclerosis without the patient's subjective discomfort. Unless the coronary vessels are involved, he experiences little distress in his chest. At most, he feels slight substernal oppression or discomfort after running or after climbing stairs.

Objectively, examination of the heart may reveal a loud second aortic sound, a systolic murmur of varying intensity, and active supra-sternal pulsation indicative of an elongation of the thoracic aorta.⁶ Electrocardiographically, there may be no changes at all or, at most, lowering of the T wave in Lead I after exercise (Master's test), slight ventricular preponderance indicative of coronary insufficiency and, occasionally, a diphasic T in Lead I or Lead II. These findings may be present at one examination and absent at another.

An x-ray examination discloses moderate dilatation of the aorta, particularly bulging of the ascending aorta, and in some instances one discerns, even at onset, small calcified plaques or patches in the wall of the aorta.

During this stage, a physician's attention to the symptoms is very important in order to prevent the serious sequelae of the disease. Without alarming him, he must caution the patient against doing anything that causes discomfort. The patient is not to give up his work, however, but is to slow his pace, never rush and never climb stairs unnecessarily. If he must do so, his progress is to be slow. Emotional upsets are to be avoided.

With care all symptoms may disappear and years pass without further disturbance.

INVOLVEMENT OF THE CORONARY ARTERIES

As the coronary artery becomes involved, symptoms begin to be pronounced. Effort angina appears. The patient cannot walk against the wind or run or enter a crowded room without feeling oppression in the chest so marked that he must rest for relief. After a few min

utes, the oppression subsides. Mental excitement brings on a similar attack. There is slight shortness of breath.

Some patients with sclerosis of the aorta and of the coronary arteries are distressed by severe burning in the back of the chest, less often in the front of the chest. However, burning beneath the sternum is more often a symptom of luetic than of sclerotic aortitis.

Angina Pectoris.—Eventually attacks of real angina pectoris occur, relieved only by nitroglycerin. The pulse rate *may* be increased. During the attacks of angina pectoris the blood pressure is markedly, though transiently, elevated, the systolic pressure rises from 150 or 160 to 180 or 200, but the diastolic pressure remains more or less unaltered.

Angina pectoris is no longer the cause for dread that formerly it was. Patients can lose their attacks and live in comfort for many years thereafter, if careful. *Mental excitement can be even more damaging than physical exertion*, this makes peaceful living indispensable in therapy. As the great Hunter once said, "Any rascal who excites me is liable to terminate my life." A moment later, as though to prove his words, he became terribly excited during a meeting of the medical board, stalked into the next room where he had a severe attack of angina pectoris, and died.

Coronary Thrombosis—That advanced coronary sclerosis with angina pectoris and hypertension can lead to coronary thrombosis with its serious consequences is well known. Of great importance, also, is the effect of arteriosclerosis upon the function of the heart (see Congestive Heart Failure).

When coronary thrombosis occurs, the patient experiences sudden agonizing pain in the substernal region, radiating to the back and left arm, or to both arms, occasionally causing numbness of the arm and fingers. Even 0.03 gm. of morphine may fail to relieve the pain, and the dose has to be repeated. With subsidence of the pain there develops a sensation of heaviness in the precordial region and of pressure behind the sternum, persisting for hours or, in some cases, for days.

Marked epigastric distress and vomiting are among the gastric symptoms that are always present. They may be so in the foreground as to lead to a mistaken diagnosis of acute abdominal catastrophe. Collapse is almost instantaneous—there is a sharp drop in systolic pressure (100 or less), cold perspiration, a rapid feeble pulse, extreme restlessness and, in some cases, a marked diminution of the urinary output. In many cases, left ventricular failure causes dyspnea, orthopnea and congestion of the lungs, followed by pneumonia or edema of the lungs, in others, pulmonary infection occurs or collapse of the lung due to inhibited mobility of the diaphragm.

If the patient survives, the collapse manifestations abate within a few hours, the temperature rises to 103° or 104° F., and leukocytosis occurs (12,000 to 20,000). There is a rise in the nonprotein nitrogen in the blood and there may be a diminution in the sodium chloride

Some authors have reported transient hyperglycemia. The systolic pressure rises, but it is never quite as high as it was before the attack. After two or three days, the temperature and white blood cells drop to a normal level.

Should an infarct occur in the anterior part of the left ventricle near the apex, pericarditis follows in about half the cases. This is characterized by increasingly severe pain over the precordium and a loud, usually transient, friction sound over the apex, occasionally over the entire heart. This is not present in cardiac infarction as a result of thrombosis in the posterior branch of the coronary artery.

It is not at all rare for emboli to be carried from the infarcted area to distant parts causing hemiplegia or even necessitating amputation of an extremity unless quick embolectomy is performed.

If there is thrombosis in the right coronary artery with extensive cardiac infarction, the clinical picture is that of right-sided heart failure (*q v*). The liver is enlarged and the patient suffers severe pain over the hepatic region owing to stretching of the liver capsule. The complexion is subicteric and vomiting is frequent. The venous pressure is markedly increased.

When infarction occurs in the septum the symptoms are those of infarction elsewhere except that in addition there is a loud, harsh, systolic murmur over the entire precordium as well as posteriorly. Electrocardiographically there may be evidence of left bundle-branch block.

If the infarction affects the bundle of His, actual heart block occurs. Sinus bradycardia and transient auricular fibrillation and, in very severe cases, pulsus alternans are not uncommon. When only a branch of the bundle of His is involved, right or left bundle-branch block occurs. If the ramifications are invaded there is intraventricular conductivity disturbance (arborization or intraventricular block) as noted by Oppenheimer and Rothschild.⁹

For several days following collapse, the heart sounds are embryonic in character and gallop rhythm is not infrequent.

The electrocardiographic findings are characteristic of left coronary thrombosis. There is an elevation of the R-T segment in Leads I and II, depression of the R-T segment in Lead III and an elevation of the R-T segment in Lead IV. After the patient recuperates, the R-T segment in Lead I becomes an inverted T. In right coronary thrombosis, there is a depression of the R-T segment in Lead I and an elevation of the R-T segments in Leads II and III.

As the patient improves the R-T segment in Leads II and III may become an inverted T complex.

During the early stage, there may be no electrocardiographic findings other than an elevation of the R-T segment in Lead IV or II and marked inversion of the T complex in Lead IV (Goldbloom¹⁰).

More rarely the thrombosis occurs in a small coronary vessel, giving

rise to severe angina pectoris or to sudden myocardial failure. If areas of fibrosis develop in the left ventricle, acute edema of the lungs may set in, or there may be progressive myocardial failure characterized by increasing dyspnea on effort, congestion of the lungs, and susceptibility to pulmonary infection.

Another form of thrombosis is that which occurs in the large coronary arteries and causes no pain (*coronary thrombosis sine dolore*), as in a series of cases reported by Boyd and Werblow.¹¹

Occasionally, there are premonitory symptoms of coronary thrombosis, namely, a sensation of substernal pressure for days or of pain in the left shoulder simulating rheumatism for weeks before the coronary disaster.

Therapy—The treatment of acute coronary occlusion is primarily that of shock. Morphine is to be given in sufficiently large doses (0.03 gm) to stop the pain. If there is the slightest tendency to edema of the lungs, atropine (0.0006 gm) should be given with the morphine. When obtainable, the rapid nasal administration of oxygen is of the utmost importance. The oxygen tent is not essential, indeed, it may be very disturbing.

During the height of shock caffeine (0.5 gm) should be given, and not more than 50 to 100 cc of 10 per cent glucose should be administered slowly by the intravenous method. If the pulse pressure is only 20 or 30, and the systolic blood pressure is extremely low, the patient should be given intramuscularly 0.5 to 1 cc of 1:1000 adrenalin chloride twice or three times daily. This is to be given *without glucose*, and is to be discontinued as soon as the extreme degree of shock improves. If heart block is present with a pulse rate of less than 30, the adrenalin may be life-saving.

Fluids by mouth should not be forced, particularly if there is abdominal distention. Should it be necessary to replace fluid lost from the body, due to excessive perspiration, it is best to give it by hypodermoclysis. 200 to 250 cc of normal saline solution, repeated in twenty-four to forty-eight hours.

Quinidine is advocated by some authors,¹² but we restrict it to cases of coronary thrombosis accompanied by fibrillation without evidence of congestive heart failure. Then we prescribe 0.15 gm of quinidine three or four times daily. Should the patient tolerate this well, the total daily dosage is increased to 0.5 or 0.6 gm. We have found it very helpful, after the second or third week, in a dose of 0.15 gm combined with metaphylline 0.15 gm, and 0.01 to 0.03 gm of phenobarbital two or three times a day. Gold and his co-workers,¹² however, do not believe that metaphylline has a beneficial effect. When fibrillation ceases, quinidine should be immediately discontinued until one is absolutely certain that the cardiac infarction has healed. Otherwise, there is still danger of embolus.

If Cheyne-Stokes breathing is present, marvelous results may be

obtained by the intravenous administration of euphylline, 0.3 to 0.5 gm

When there are signs of *congestive heart failure plus auricular fibrillation and a rapid pulse*, or *tachycardia without fibrillation*, 0.35 digitalis, should be administered, repeated within 3 or 4 hours, and continuing 0.1 every six hours until the pulse rate returns to normal. It should be immediately discontinued if toxic effects, particularly coupling rhythm, are noted.

If the patient is vomiting, has an enlarged liver, and a rapid pulse rate, digitalis should be given intramuscularly, intravenously or intrarectally, unless these symptoms are known to be due to the toxic effect of the digitalis. In that case it is to be discontinued.

When giving digitalis by rectum, it is important that it be preceded by a cleansing enema of 16 ounces of lukewarm water in which one teaspoonful of salt has been dissolved, this is intended to wash out the small bowel. The digitalis is then administered in 50 cc of starch water to which one teaspoonful of salt has been added, the ratio being 7.5 cc. of tincture digitalis to 60 cc of starch water. The nozzle should be inserted at least 4 or 5 inches into the rectum in order to reach the internal hemorrhoidal vessels and the digitalis thus absorbed through the portal circulation. As soon as the liver diminishes in size, digitalis by mouth may be resumed.

The patient should not be permitted out of bed until six weeks have elapsed and not before the sedimentation rate has returned to normal. During the first three weeks he must be kept entirely at rest, followed by gradual propping up and light massage to improve peripheral circulation. During the first two weeks the diet should have a very low caloric content (800 to 1000 gm).

Rupture of the Heart—A rare complication of coronary thrombosis with cardiac infarction is rupture of the heart. If the patient does not die at once, hemipericardium results. There is severe dyspnea or orthopnea, extreme pallor and almost inaudible heart sounds, embryonal in character. The cardiac rate is very rapid and percussion discloses flatness extending on the right beyond the border of the sternum, and on the left, beyond the midaxillary line. Examination by portable x ray is of great diagnostic aid showing an immense heart shadow with loss of the cardiac outline and, conspicuously no evidence of congestion of the lungs.

CARDIAC FAILURE

In many instances of hypertensive heart disease there is a gradual diminution of the cardiac reserve. The first symptoms are shortness of breath and cardiac palpitation, following activity that only slightly exceeds normal effort. These subjective symptoms are far more informative than functional tests that require the patient to do something that is not customary at a time when he is apprehensive. Many of these patients tire much more quickly than formerly and their

sleep is disturbed by dreams, dyspnea or Cheyne-Stokes breathing, even while sleeping with an extra pillow under the head. There is nycturia and more urine is passed at night than during the day.

If the early symptoms are not heeded, the dyspnea increases and edema of the lower extremities occurs, disappearing at night. Palpitation and extrasystoles are troublesome. There are rales in the bases of the lungs, and a systolic murmur can be heard at the base and sometimes at the apex of the heart, even though the rate is not increased. A persistent murmur in these areas signifies sclerotic changes in the aortic and mitral valves. The second aortic sound is ringing. The left ventricle and aorta, particularly the arch and descending aorta, are enlarged, and not infrequently x-ray examination reveals deposits of lime in the aorta, less often in the aortic and mitral valves.

When the deposit of lime in the aortic valve is extensive, there is aortic stenosis, giving rise to a loud, harsh, systolic murmur over the aortic region and sometimes a thrill on auscultation and palpation. Suprasternal pulsation is diminished or absent, but there is increased pulsation in the supraclavicular region.

Fatal emboli—cerebral or mesenteric—may occur most unexpectedly.

Not infrequently, *left ventricular failure* manifests itself first by night dyspnea, the patient awakening suddenly and rushing to the window for air. He is cyanotic and covered with cold perspiration. In some cases the dyspnea is bronchial asthmatic in type, as indicated by prolonged loud wheezing on expiration. During the attack the systolic pressure increases to 200, 250 or more, due undoubtedly to asphyxia, and the second aortic sound is louder than the second pulmonic.

If there is persistent auricular fibrillation, particularly if the basal metabolic rate is elevated, differential diagnosis from cardiac dysfunction due to thyrotoxic disease is difficult. In the latter condition, the basal metabolic rate is persistently elevated, whereas in arteriosclerotic hypertension the basal metabolic rate varies, often coming down to normal in the course of weeks in spite of the persistent fibrillation. In thyrotoxicosis, also, the cholesterol in the blood is usually low (140 to 150 mg per 100 cc) in contrast to arteriosclerotic heart disease in which it is either normal or elevated. Finally, the thyrotoxic patient is restless, perspires profusely, and has warm hands and feet. The arteriosclerotic hypertensive patient, even while perspiring, is cold.

Therapy.—It is essential for the patient in the early stage of circulatory failure to understand that he can live a normal, useful span of life if he lives according to his heart's possibilities and not according to his desire. The first and most important requirement is adequate physical and mental rest. If there is increasing dyspnea or edema of the extremities during the day (disappearing at night), the patient should be put to bed for eight or ten days and his fluid intake should be restricted. Following this, there should be one hour of rest every afternoon and one full day in bed every ten days.

Sleep is to be encouraged by mild hypnotics (phenobarbital preparations amytal, and so forth)

If there are annoying extrasystoles, quinidine sulfate, 0.15 gm, twice daily to test tolerance, with gradual increase to 0.3 gm, should be given. For patients still fairly well compensated, but in whom there is fibrillation quinidine sulfate, 0.3 gm three times a day, is a specific. After the patient has improved, he should get one 0.2-gm capsule of quinidine sulfate each day for an indefinite period.

Should the patient suffer from the asthmatic type of dyspnea which does not subside spontaneously, the therapeutic indications are morphine, 0.015 gm, and atropine, 0.0006 gm, hypodermically. Despite the high blood pressure, adrenalin, 0.5 to 1 cc, intramuscularly, may also be necessary to relieve the asthma. In many instances aminophylline, 0.3 gm given intravenously before retiring is more effective than any other drug.

CONGESTIVE HEART FAILURE

In advanced congestive heart failure, there is dyspnea without exertion or there may be orthopnea so that the patient must sit up when in bed. There is usually a preceding history of a cold or a respiratory infection with elevation of temperature. Rales are present over both lungs, very often even small areas of consolidation due perhaps to inflammatory changes or repeated lung infarcts. There is considerable cyanosis. The heart is enlarged. There is active epigastric pulsation. The heart sounds are usually increased in rate with accentuation of the second aortic sound. A systolic murmur is heard at the apex and base of the heart, and there are frequent extrasystoles.

In many cases the blood pressure is markedly lower than the previously existing high figure. It is quite important in such instances to determine by the blood pressure reading whether a pulsus alternans is present. This is done by taking the diastolic blood pressure and when the lowest point is reached if one pulse beat is heard and the next one falls out pulsus alternans is present. This is significant because pulsus alternans is a sign of grave prognosis in congestive heart failure. Gallop rhythm likewise is of grave prognosis.

X-ray examination discloses an enlarged heart with marked densities of the lung shadows from hila to axilla and almost down to the diaphragm, sometimes simulating diffuse pneumonic infiltration.

The patient's temperature is moderately elevated (100° to 102° F) as a rule, due in most cases to actual inflammatory changes in the lung. The administration of penicillin is indicated.

Management—Rest, restriction of fluids and a diuretic are indicated. The diuretic should be in the form of the slow intramuscular injection (1 cc) of mercupurin preceded by ammonium chloride in chocolate-coated tablets, 2 gm every two hours for fifteen doses. The ammonium chloride is given to prevent alkalosis. The next day 1 cc., or

ness or a nocturnal burning sensation are experienced in the lower extremities. There is diminished pulsation in the femoral, popliteal, posterior tibial and dorsalis pedis arteries.

An aneurysm may rupture, as exemplified in a woman in her fifties who suddenly complained of severe pain in the upper abdomen. She had lost weight and when seen was nauseous and vomited frequently. She was very pale due to secondary anemia and her blood pressure was 200/100. The heart was enlarged and a systolic murmur was noted over its base. Active pulsation of the abdominal aorta with a bruit was also present. X-ray examination of the gastrointestinal tract in the hospital was negative. One week later, she developed abdominal distention, facies hippocratica, and other manifestations of collapse. Our clinical diagnosis of rupture of the abdominal aorta was confirmed at autopsy twelve hours later.

Sclerosis occasionally produces narrowing of the abdominal aorta, causing diffuse abdominal pain, pulsation, and marked distention especially of the cecum and transverse colon. A loud systolic murmur can be heard over the cordlike abdominal vessels. Meteorism may be as marked as in peritonitis except that distinct sounds may be detected by auscultation.

Thrombosis of the abdominal aorta is generally followed by gradual obliteration interfering with the circulation of the lower extremities. If a saddle thrombus occurs there is extreme pain in the lower extremities and loss of pulsation in the femoral vessels. When canalization takes place there is complete obliteration, rapidly followed by gangrene of both lower extremities.

MESENTERIC THROMBOSIS

If thrombosis occurs in a mesenteric artery of large caliber, the symptoms are sudden, colicky pain in the abdomen, singultus, and non-fecal vomiting. Hematemesis is rare, but may occur due to regurgitation of blood from the intestines into the stomach. About half of the patients have bloody stools. The loss of blood may be so excessive as to cause death. When it does not, obstipation almost to the degree of ileus and extreme pallor are marked. In spite of the apparent collapse the temperature is elevated, the blood pressure very high, and the pulse rapid. Peristalsis may be visible over the obstructed part of the colon.

The pain is so intense that it cannot be relieved by narcotics. Except in rare instances of spontaneous recovery, the patient moans continuously until death releases him from his agony.

INFARCTION OF THE INTESTINES

If infarction occurs in the lower colon, there is severe intestinal hemorrhage, if it occurs higher up, hemorrhage from the stomach is present, if in the upper part of the small intestines there is intestinal

obstruction with azotemia leading to death within thirty four to thirty six hours. In rare instances, gangrene ensues causing perforation and peritonitis. Still more rarely blood oozes from the intestines into the peritoneum, causing hemorrhagic ascites.

When there is thrombosis of a small vessel, the patient suffers acute, colicky pain and moderate abdominal distention, the cause of which can often be ascertained only on the operating table. Treatment is always surgical and is generally ineffectual.

ARTERIOSCLEROTIC CHANGES IN THE SMALL INTESTINES

The chief symptom of arteriosclerotic changes in the small intestines is severe intestinal colic (*dyspragia arteriosclerosis intestinalis*, Ortnier). This is accompanied by marked hypertension. The pain occurs abruptly and reaches its maximum in a minute or two, and subsides within ten or fifteen minutes, sometimes it lasts for several hours or a week. It may cause the patient to faint, especially if it is confined to the upper abdomen. Episodic vomiting occurs for days causing the patient to become emaciated and pale. Obstipation and abdominal distention are marked.

The symptoms improve suddenly, as a rule after several days or weeks. The patient is then comfortable for months—until another attack occurs.

X ray studies of the colon often disclose marked distention of the ascending colon, and spasm of the descending colon.

Rupture of sclerosed intestinal vessels is much more frequent than is rupture of the small gastric vessels. It causes frequently recurrent hemorrhage from which the patient usually recuperates rapidly.

SCLEROSIS OF THE ARTERIES OF THE STOMACH AND DUODENUM

If a patient with peptic ulcer is also afflicted with arteriosclerosis he may sustain severe gastric hemorrhage terminating fatally. This is rare, fortunately. In other cases the nutrition of the wall of the stomach may be so disturbed as to favor perforation. The largest perforated ulcers have been found in patients with arteriosclerosis.

When the vessels in the gastric mucosa are sclerosed, localized trophic changes occur as a forerunner to gastritis. The patient complains of persistent pressure or pain in the upper abdomen that is independent of meals though aggravated by food. Other symptoms are nausea and loss of appetite.

SCLEROSIS OF THE ARTERIES OF THE PANCREAS

Extensive arteriosclerosis of the pancreas need cause no digestive disturbance though pain in the upper abdomen is usually present. Other symptoms are mild polyuria and polydipsia. Remarkably enough, all tests for external secretion disturbance such as the amylase and lipase tests are conspicuously negative.

If the sclerotic process involves the tail of the pancreas, actual diabetes may result, presenting glycosuria and moderate hyperglycemia, or hyperglycemia without glycosuria. No acetone or diacetic acid is in the urine. Such a patient rarely requires insulin, in fact, he is insulin-resistant.

Moderate restriction of carbohydrates and the intramuscular or oral administration of vitamin B will generally control such diabetes. Some authors (notably Biskind and Schreier, and Jolliffe) believe that the primary disturbance in these cases lies in the liver, and that this interferes with vitamin B utilization and carbohydrate metabolism. We, too, have encountered cases where there was some evidence of disturbed liver function. Stomatitis, gingivitis and cheilosis, which are generally present, improve rapidly under vitamin B therapy.

The following is an illustrative case.

The patient was a woman, aged 68, with a negative history except for hypertension. She developed moderate abdominal pain accompanied by bowel movements that were so large as to be out of all proportion to her food intake. The character of the stools—glistening and rich in fatty acids—suggested pancreatic disturbance. Her blood sugar was 260 mg per 100 cc and the glycosuria was 1.6 per cent. X-ray examination of the gastrointestinal and biliary tracts was negative. The clinical diagnosis was chronic pancreatitis.

The patient reacted very poorly to insulin. Small doses of protamine insulin were enough to throw her into shock. So it was decided to keep her on a restricted diet and to administer large doses of pancreatin (2 gm) and trypsin (1 gm) three times daily. The improvement was almost immediate, her stools became less bulky and her bowels moved only once a day. The carbohydrate intake, then, was increased without ill effect. The sugar in the urine was 0.5 to 1 per cent in twenty-four hours. The blood sugar did not rise above 130 mg per 100 cc. She gained weight. She was also given liberal intravenous injections of vitamin B (30 to 50 mg) daily.

SCLEROSIS OF THE SPLENIC ARTERIES

Arteriosclerotic changes in the spleen are very common, leading to small areas of infarction in the kidney without symptoms during life. Thrombosis of a large splenic artery with infarction occurs occasionally, followed by severe abdominal pain radiating to the left hypochondrium and shoulder. Within a few days the spleen enlarges to two or three times its normal size, and remains enlarged even after canalization of the thrombus. There is secondary anemia with mononucleosis and leukopenia. The liver is very often enlarged. Occasionally the thrombus leads to severe infarction, suppuration of the spleen, and sepsis unless splenectomy is performed.

RENAL SCLEROSIS

Only rarely does the sclerotic process extend to the arterioles of the kidneys leading eventually to primary contracted kidney. Thrombosis of a vessel in the renal cortex is somewhat frequent, leading to small

areas of infarction Neusser believed that periodic pain in the lumbar region, particularly in one loin, was due to such a cause

If there is thrombosis of a large artery it is followed by severe abdominal pain, diffuse at first, then localized both anteriorly and over the loin of the affected side with radiation to the uterine, urinary bladder, and testicles or vulva Systemic symptoms may be present, notably elevation of temperature and rapid respiration, due to congestion of the lungs, simulating bronchopneumonia Physical examination reveals percussion, tenderness over the affected loin and sometimes rigidity of the lumbar muscles On deep palpation the kidney can be felt and is tender There is slight pain on urination Cystoscopy establishes the diagnosis, for the urine invariably contains a large number of red blood cells Occasionally a blood clot is dislodged from the ureter during the cystoscopic examination and the symptoms are relieved Surgical intervention is necessary for progressive infarction, the outcome of which unfortunately is rarely successful

The fact that the arterioles of the kidney are seldom involved explains why, even in the presence of diffuse generalized arteriosclerosis with hypertension marked renal insufficiency and uremia are extremely rare This is a point of differentiation from malignant essential hypertension and is significant for management.

UNILATERAL ADRENAL ARTERIOSCLEROSIS

Recently Edelman¹⁷ reported a unique case of huge renal lipoma and quoted a similar earlier but fatal case described to him in a personal communication from Dr A. Hyman and which was one of the earliest cases ever reported. Postmortem examination proved death to be due to arteriosclerosis of the adrenal artery which has given rise to adrenal hemorrhage.

The patient reported by Edelman gradually developed abdominal pain which increased and became localized in the upper quadrant of the abdomen, external to the umbilicus about 2 inches below the costosternal margin. This area was tender to touch but rigidity was absent. The presence of copious vomiting which was projectile at times at first suggested intestinal obstruction However the picture was clearly the classical one of spontaneous perirenal hemorrhage sudden, sharp pain in the kidney region followed by nausea and vomiting abdominal distention, and other signs of perirenal irritation still without fever Then came pallor prostration, and other signs of internal hemorrhage together with the appearance of a perceptibly enlarging tumor mass in the loin

Exploration verified the diagnosis hemorrhage into the perirenal tissues was found to have occurred. Because of the prompt surgery the patient recovered.

ARTERIOSCLEROSIS OF THE EXTREMITIES

Arteriosclerotic changes in the extremities particularly the lower ones, occur late in life and are slow in progress One of the first symptoms is the fact that walking is commenced with effort, but after a few steps fatigue disappears A short time later it reappears and con

tinues until the patient rests. A tired feeling in the legs is particularly troublesome at night. The patient often exclaims, "I can't find room enough in the bed for my legs!" The surface temperature of the limbs is cool and erythromelalgia is not present. Pulsation in the dorsalis pedis and posterior tibial vessels is undiminished while the oscillographic readings are normal.

If gangrene develops, amputation becomes necessary. For this reason it is especially important to differentiate between arteriosclerosis of the extremities and thromboangitis obliterans. For the latter condition palliative treatment is effective. A differential feature is that thromboangitis obliterans occurs during early life, as a rule, and at first walking is not tiring. After a block or two, pain occurs suddenly, and disappears as quickly when the patient rests.

CEREBRAL ARTERIOSCLEROSIS

In many arteriosclerotic hypertensive patients, cerebral symptoms are apt to be more prominent than cardiac symptoms. This is particularly true of arteriosclerotic women during the menopause. As a rule, the symptoms vary in degree. Although there is no actual pathology of the brain (for which reason Fishberg calls it encephalopathy) such as softening or hemorrhage, the clinical manifestations indicate considerable disturbance in cerebral function. This is easily understood because the brain, more than any other organ, is highly sensitive to anoxia. Even transient arterial spasm or the slightest interference with capillary function of the brain suffices to give the impression that a serious lesion is present. This explains, also, how remissions occur during which brain function is again present. One may, therefore, divide the brain disturbance due to arteriosclerosis into a mild, reversible state, and an irreversible state.

Reversible State.—The patient may have *transient lapse of memory*, even amnesia. He may experience frequent spells of *transient weakness* in the hands so that he cannot hold an object in either hand. Or he may experience such weakness in the lower one or the other lower limb, or both. This may last a few minutes or pass at once. *Speech may be temporarily affected*. The psychical effect upon the patient is usually very bad. Therefore, it is important for the physician to know the nature of these attacks in order to calm the patient by his assurance that the attack is (probably) transient. The physician as well as the patient may be particularly alarmed by the fact that during the attack the blood pressure soars out of all proportion to the previous pressure. For instance, if the systolic pressure has been 180 to 200 it may rise to 250. The increase in diastolic pressure is not so marked. This increased pressure is probably due to a temporary increase in intracerebral pressure or to overstimulation of a vasomotor center in the medulla oblongata. Within a minute or two, the blood pressure

returns to its previous level and the loss of sensation in the limbs or of speech disappears

It is important to remember that, if the patient is calmed and reassured, *such an attack may not repeat itself for many years, perhaps not at all*. It need not be a forerunner of cerebral hemorrhage or thrombosis. This is emphasized because we know from experience that some physicians, when confronted by a patient in such a state, alarm by their manner if not by their words both the family and the patient with the implication that the attack is the prelude to early fatality. We agree that this *may* be so but it is not necessarily so.

Labyrinthian Disturbances—Headache, vertigo and dizziness may be so annoying that the patient has to remain in bed for days or weeks before surcease occurs. Even more disturbing are nausea and vomiting. These labyrinthian disturbances can easily be differentiated from those in Ménière's disease because in the latter there is seldom any rise in blood pressure. When there are an associated pallor, vomiting and an auditory disturbance in one ear, with deafness ensuing, the other symptoms of Ménière's disease disappear. The vertigo that occurs in arteriosclerosis (more common in women than in men) is not accompanied by disturbed hearing. However, there is one distressing symptom that may be presented in both ears day and night and that is *tinnitus aureum*.

Eye Changes Examination of the eyes is of the utmost importance for, occasionally, arteriosclerotic changes are detected in one or both eyes. These may be reversible unless the central retinal artery is involved, in which case vision remains disturbed.

A thorough examination of the eyes is particularly indicated in early arteriosclerosis because by the judicious use of dicumarol or heparin a clot may be dissolved, thus preventing permanent disturbance of vision. However, a thorough investigation of the prothrombin time by Quick's method as well as of the coagulation time must be made before either of these drugs is used in order not to induce a diffuse hemorrhage in a susceptible patient.

Irreversible State.—**CEREBRAL INVOLVEMENT**—As the age of the patient advances so do the evidences of cerebral involvement. The patient becomes abusive and has hallucinations. If the patient is not too old, many of the symptoms may disappear with care. In an elderly person they cannot be halted. We now have a 64 year old patient who has generalized arteriosclerosis, high systolic blood pressure, marked cardiac symptoms particularly of right sided heart failure, enlargement of the liver, edema of the lower extremities and increased venous pressure. The electrocardiographic examination has disclosed cardiac damage and right axis deviation. Following rest, medical treatment and dehydration for the cardiac symptoms he developed cerebral manifestations including hallucinations, delusion and wrist drop the right arm. Then he developed marked Cheyne-Stokes br

Yet he continues to live, having improved in some respects. The wrist drop has disappeared. The specific gravity of the urine is normal and is of sufficient output. Although at first the nonprotein nitrogen rose to 70 mg, it has dropped to 60 mg (extrarenal azotemia). But as the Cheyne-Stokes breathing is still present, he may die suddenly as is so often the case in protracted Cheyne-Stokes breathing.

SUBARACHNOID HEMORRHAGE—The patient with irreversible arteriosclerotic symptoms suffers from severe headaches, particularly occipital, as in the case of the late President Roosevelt. He loses his memory and sometimes his speech, particularly just before subarachnoid hemorrhage. This calamity may occur even without hypertension, as a result, for instance, of aneurysmal dilatation, and in fairly young people. It need not be fatal if lumbar puncture is done sufficiently early to remove the bloody fluid from the spinal canal and thus relieve intraspinal and intracerebral pressure. In the arteriosclerotic patient with hypertension, however, early fatal termination after such a hemorrhage is the rule. Consciousness is lost at once, the neck becomes rigid, and even the earliest lumbar puncture can give no more than transient relief.

Cerebral hemorrhage affecting the internal capsule, either on the right or left, is known to almost every clinician. Without premonitory symptoms, an individual, previously not even considered ill, may rise from his bed in the middle of the night, try to raise his arm, suddenly lose consciousness, and begin to breathe stertorously. There is paralysis of the side of the body opposite that in which the hemorrhage occurred.

In a few of these alarming cases the patient improves, with motion returning first to the arm and then to the leg, but even though he may survive for many years there is some residual permanent paralysis.

More often, the symptoms are rapidly progressive. The affected side of the face becomes flushed and the temperature of the affected side of the body increases. Cheyne-Stokes breathing occurs and death occurs within a few minutes, or hours. In rare cases, the symptoms continue for twenty-four to forty-eight hours as edema of the lungs and pneumonia develop to a fatal conclusion.

Cerebral Thrombosis due to Hemorrhage—Following cerebral hemorrhage sudden thrombosis may occur with instantaneous loss of consciousness and paralysis of the side opposite that in which the thrombosis occurs. One feature, if it has been present, is a clue to diagnosis during life. That is, the existence of severe headaches for weeks prior to the loss of consciousness, accompanied by nausea, vomiting and loss of appetite. Naturally, actual diagnosis is not important because softening of the brain with marked cerebral disorientation will set in, regardless. Even though the functions of the extremities and speech may be restored, with consciousness returning, the brain's deterioration cannot be halted.

False Tumor of the Brain—The symptoms of headache, transient paralysis and other disturbances of the body have sometimes pointed to tumor of the brain. Cases have been reported pointing so conclusively to such a lesion that operation has been performed and yet the surgeon has been unable to find a tumor. Postmortem examination has revealed the condition to have been only severe arteriosclerotic involvement of the brain.

ARTERIOSCLEROSIS OF THE SPINAL CORD

Although arteriosclerosis of the spinal cord is rare, such cases have been reported. Waltman,¹⁸ for instance, analyzed fifty nine cases that had been studied at postmortem, and found degeneration of the cord and lateral posterior funiculi which had caused symptoms of subacute combined degeneration during life. This is of great importance because such patients with moderate anemia may fully resemble patients with pernicious anemia.¹⁹

Many authors including Dana²⁰ in the United States and Gowers²¹ in England, have attributed paraplegia in the aged to sclerotic changes in the small arteries and arterioles of the spine. Some authors have even spoken of the arteriosclerotic spinal arteries as a cause of symptoms simulating *tubercles dorsales*.

The sclerotic changes found at postmortem examination are usually in the intima and media, seldom in the adventitia of the vessels of the spinal cord. In some cases periarteritis only is found.

THE DIETETIC AND GENERAL CARE OF PATIENTS WITH ARTERIOSCLEROSIS

General Care.—The dietetic care of the arteriosclerotic patient is of highest importance but there are also certain rules of general care that must be followed. These are:

1. The patient must have adequate rest, a good sleep each night being particularly important. Barbiturates are by no means necessary being reserved for use only when absolutely needed. Barbiturates while relieving temporarily become habit forming when used liberally.

2. Carbonic acid baths carefully managed, are beneficial. Their effect upon the patient with high blood pressure can not be overestimated however.

He should drink at least every other day 2 teaspoonfuls each of sodium sulfate and magnesium sulfate dissolved in a glass of cold water, to be sipped slowly

It is a well known fact that in many diseases a patient will have a marked disturbance in cholesterol metabolism, the cholesterol being as high as 900 mg per 100 cc of plasma. Yet these patients may not have hypertension. In other conditions, for instance thyrotoxicosis, the patient very often has hypertension with a low cholesterol figure. So if an arteriosclerotic patient has both hypertension and a high cholesterol figure, his fat intake is to be reduced, and he should *not* have a diet that is rich in cholesterol. It is well known that many diabetics, particularly when obese, have a tendency to arteriosclerosis and also to coronary artery disease. It is therefore essential to bring about a reduction in the weight of such patients. In order to do this the restriction of fat intake is highly important. Of even more importance is the elimination from the diet of egg yolk, brain, kidney, liver, pancreas, thymus and salmon roe as these foods are richest of all in cholesterol. Beef, mutton, potatoes and most vegetables contain little cholesterol.

Some authorities favor decreasing the intake of milk because of milk's excessive calcium content. However, in adult life the intake of milk is seldom so excessive as to require restriction. We cannot imagine that the milk taken by an adult can be so detrimental as to cause arteriosclerosis or hasten the sclerotic process.

The relationship of cholesterol metabolism to arteriosclerotic changes in the aorta has been dwelt upon by many authors beginning with Aschoff. Leary⁸ demonstrated that the feeding of lipids to the rabbit caused deposits of cholesterol in the arteries, favoring sclerotic changes which he believes are analogous to those in the human. Other clinicians^{22, 23, 24, 25} have concurred with this opinion. It is important not to overlook the fact, however, that not all arteriosclerotic patients have high cholesterol values in the blood. On the other hand, where the blood is very rich in cholesterol as in myxedema, lipoid nephrosis and Hand-Schuller-Christian disease, there need be no arteriosclerosis. One can only reason that in an individual with degenerative changes in the blood vessels of an arteriosclerotic nature, the excessive intake of cholesterol-rich food may increase the irritation of the vascular system and hasten the arteriosclerotic process.

Boas and Adelsberg²⁶ have recently again brought up the question of hypercholesteremia in association with arteriosclerosis. A number of cases of arcus senilis and hypertension in middle aged individuals were discussed, these patients had metabolic disturbances and hypercholesteremia. Here again one must recall that cholesteremia is not essential to the presence of arteriosclerosis. It seems rather to be a question of some local metabolic disturbance in the patient's blood vessels that predisposes them to irritation and arteriosclerosis upon the deposition therein of cholesterol.

In regulating the diet of the arteriosclerotic patient one must be careful not to deprive him of necessary vitamins, particularly vitamin A. Regardless of its calcium content, the patient should not be asked to abstain from it.

Neither should salt be excluded from the diet because this would interfere quantitatively with the hydrochloric acid in the stomach. The hydrochloric acid after middle age has a tendency to be diminished anyway. But the patient should not eat salty foods like herring and bouillon which would cause his water intake to be more than his minimal requirement.

The aging patient can usually accommodate himself with ease to foods with a minimum of cholesterol and to the beneficial limitations of rules of living mentioned above.

SUMMARY

I have dwelt at length on the symptoms and complications of arteriosclerosis associated with hypertension because of their importance in clinical medicine. Too often they are overlooked, being overshadowed by the prominence occupied today by essential hypertension.

Many of the symptoms that occur in association with hypertension due to arteriosclerosis can occur, also, in essential hypertension. The difference is that the course of hypertension due to arteriosclerosis can be somewhat modified and delayed by proper management whereas that of essential hypertension is far less amenable to treatment other than surgical intervention.

In arteriosclerotic hypertension, early recognition is particularly important because of what can be accomplished by therapy, dietary and other care. This is especially true when there are circulatory symptoms. It is astonishing how well the arteriosclerotic heart responds to treatment and how life may be indefinitely prolonged when proper attention is given to the condition.

The complication of involvement of the coronary arteries by the sclerotic process leading to angina pectoris and eventually to coronary thrombosis is by far more frequent in hypertension due to arteriosclerosis than it is in essential hypertension. That is another reason for rescuing the subject from the shadow of the almost exclusive attention being paid today to a form of hypertension that is far less amenable to treatment.

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OBESE THYROIDITIS DEFICIENCY IN THE FEMALE

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THIS paper presents the author's clinical observations during a five year period (1938-1942) while treating a group of individuals who complained chiefly of obesity and symptoms related to thyroiditis deficiency, and conclusions from that treatment. Reports of similar cases in medical literature as well as laboratory and physiological experiments in the management of this condition are also evaluated and compared with the results obtained.

The triad of symptoms and signs—obesity, menstrual disturbances and symptoms of thyroiditis deficiency—in the patients studied suggested the diagnosis of "obese thyroiditis deficiency," a term favored by Engelbach. To delimit a clinical entity in this way, despite variabilities in the individual phases, has the advantage of classing in one category many symptoms and well known syndromes which at present suggest only morphological features as clinical entities and which offer many exceptions and contradictions.

Patients Studied—The fifty two female patients studied and herein presented were selected from a much larger group of patients of both sexes, of varying ages. These patients were within the age limits when full ovarian function is to be expected (Table 1) and none had a

TABLE 1—AGE AND WEIGHT RANGE

No. of Patients	Age	Weight	Average Weight
13	12-19	151-231 lbs.	181 lbs.
15	20-29	148-330 lbs.	208 lbs.
24	30-39	146-290 lbs.	192 lbs.

specific disease or pathological condition other than the glandular deficiency for which treatment was instituted. Most of the patients had been referred from other clinics where they had been under treatment for obesity and associated complaints for a varying period of time. Psychic improvement was denied by the existence of copious hospital records attesting to previous treatment by injections, pills, vitamins and hormones of all sorts without apparent benefit. Their surgical histories were negative. Twenty one of the patients were unmarried, thirty one were married and of these six were childless and twenty five were mothers of from one to twelve children.

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SYMPTOMS AND SIGNS

Obesity.—Most of the patients exhibited the typical pituitary fat distribution described by Goldzieher,¹ Hamblin,² and Beck³ and others, namely, a peculiar predisposition to fat deposits in well defined areas. balloon tire hips, apronlike sagging of the lower abdomen, conspicuous pads of fat on upper arms and thighs especially the inner aspects. The actual morphology varied according to the patient's age at onset, duration of the condition, preexisting physiological status, and prominence or severity of the sequelae of hypopituitarism, namely, secondary hypothyroidism and hypogonadism.

Menstrual Disorders.—The patients were divided into four groups according to menstrual disturbances. Where there were dual characteristics, the more prominent dictated the category in which the patient was grouped.

Dysmenorrhea (Eleven Patients, Table 2) —Patients who complained of severe pain immediately before, at onset, and/or during menstrual flow were considered dysmenorrheic. Associated menstrual phenomena were

Five patients	oligomenorrhea and hypomenorrhea
Four patients	hypermenorrhea
One patient	totally irregular
One patient	nausea and vomiting at each menstrual period
Three patients	premenstrual tension

Amenorrhea (Thirteen Patients, Table 3) —An interval of three months between menstrual periods was arbitrarily chosen to differentiate amenorrhea from oligomenorrhea. Among these patients were two who had menstruated once a year only, one (Case D 12321) for eight years and the other (Case A 10911) for ten years. Many of the amenorrhea cases had been preceded by hypomenorrhea and oligomenorrhea.

Hypomenorrhea and Oligomenorrhea (Twenty Patients, Table 4) —Patients whose menses were scant, brief, and which occurred less often than normal up to three months apart were regarded as hypomenorrheic. When the interval between menses averaged less than three months, the patient was classified in the group with oligomenorrhea.

Associated symptoms were

Nine patients	premenstrual tension
Nine patients	menses at irregular intervals, the time between being more than ten days
One patient	irregular "dribbling" since the birth of a child four years before
One patient	"dribbling" for "weeks at a time" at irregular intervals

Hypermenorrhea and Polymenorrhea (Eight Patients, Table 5) — The hypermenorrheic patients complained of prolonged or profuse menses or both, those who were classified as polymenorrheic had menstrual intervals of markedly fewer than twenty-eight days. Associated phenomena were

- Seven patients premenstrual tension
- One patient : dysmenorrhea.
- One patient diarrhea.
- One patient (age 13) profuse leukorrhea.

Miscellaneous Accompanying Symptoms — The menstrual disturbances were accompanied by a host of miscellaneous symptoms. These included headache, fatigability, somnolence, emotional instability, mental sluggishness, dyspnea, precordial pain, backache, nocturia, polydipsia, polyphagia, loss of libido, hirsutism, acne and insomnia. Their incidence in the various categories of menstrual disorder is shown in Table 6.

One has to be careful when evaluating wholly subjective symptoms. Sensitivity is a personal trait. Unhappy surroundings or a difficult environment may give rise to neurotic introspection leading to neurotic symptoms. However, patients could not disguise or modify a dull, listless demeanor, drooping mouth, narrow palpebral fissures, and an utter lack of animation suggesting the haggardness or progeria of Simmonds disease. Other patients were subject to nervous irritability, emotional instability, and an alert anxiety bordering on tearfulness. These were subconscious reactions to a defeat of the compensatory mechanism, indicating an impending "nervous breakdown," behavior problems, psychoneuroses, or even psychoses. One or another of these states was noted in every patient, although varying in intensity. The milder manifestations were difficult to recognize, the mixed were sometimes paradoxical. Many patients had become apathetic as a result of prolonged, ineffectual treatment in other clinics, they were frankly discouraged clinic habitués.

Basal Metabolic Rate — We found the basal metabolic rate to be of little value as a sole criterion of thyroid involvement. The estimations ranged from minus 23 per cent to plus 50 per cent. Clinical appearance, pulse rate and blood pressure determinations had also to be considered in order to rule out hyperthyroidism. Repeated studies had to be made to check errors or nervous reactions. Engelbach¹ * * * In a series of 264 cases of thyropituitarism, male and female, has reported similar variations (Table 7).

Blood Tests — Thorough blood pressure and blood chemistry studies were not routinely possible in our overburdened, insufficiently staffed city hospital. However, a Wassermann test was performed on every patient admitted. No patient with a positive Wassermann test.

TABLE 2—DYSMENORRHEA ASSOCIATED WITH OB

No	Age, Status, Parity	Ht., Wt. in—lb	Pulse, B.M.R.	Past History	Present Menses	Present Symptoms
C 14511	28 S	63½ 229	96 +30	Menarche at 13 q 28 x 1½ Weighed 175 at 18	q 28 Dysm. Hypm. Pre T	Headache. Fatigability
C 8712	35 M 2	62½ 270	60 +31	Menarche at 12 q 28 x 6 Gained after pregnancy	q 30 x 2. Dysm. Hypm. Pre T	Headache. Fatigability Somnolence. Polydipsia. Polyphagia.
P B	24 M 1	69½ 174	78 -16	Menarche at 12 q 30 x 5 Horrible Dysm to pregnancy	Dysm. Hypm.	Headache. Fatigability Somnolence. Gaining rapidly
A 10024	17 S	65½ 196	70 -9	Menarche at 12 q 30 x 4.	Dysm. Hypm. Olgm. (7 to 12 wks.)	Headache Fatigability Somnolence. Mental sluggishness, but sutism.
B 15630	28 M 3	65½ 282	100 +25	Menarche at 12 q 28 x 3 Pregnant at age 15 then gained weight.	Dysm. Hypm. Irregular	Headache. Precordial pain. Nocturia. B P 200/110
D 12786	13 S	65 185	70 -18	Menarche at 13 q 28 x 6 Hypm Gain began at 8	Dysm Hypm. (7 days)	Headache. Polydipsia. Polyphagia. Acne. Gaining rapidly
C 13493	16 S	60½ 155	75 -4	Menarche at 13 q 28 x 5 Hypm.,* Dysm	Dysm Hypm Pre T	Severe and extensive acne of face.
D 2466	24 S	62½ 187	68 +7	Menarche at 13 q 30 x 7	Dysm. Hypm	Headache. Dyspnea. Polyphagia. Hirsutism Gaining rapidly
C 12303	31 S	60½ 210	75 +22	One ovary removed 11 yrs ago	Dysm. Nausea and vomiting	Fatigability Dyspnea.
G C	31 M 0	63 162	78 +16	Menarche at 12 q 3 to 7 weeks	Q 30 preceded by 3 days of spotting.	Mental sluggishness vague abdominal pain Sterility
A 18165	16 S	60 202	80 -3	Menarche at 12 q 3 to 7 weeks	q 30 x 7 Dysm Hypm	Headache. Mental sluggishness gain ing since age 10

Mns Pertaining to menstruation.

Dysm. Dysmenorrhoea.

Hypm. Hypomenorrhoea.

Olgm. Oligomenorrhoea.

Hypm Hypermenorrhoea.

Pre T Premenstrual Tension.

* Thyroid therapy for two years loss of 30 lbs., no change in character of menses or symptomatology

ESITY AND SYMPTOMS OF PITUITARY DEFICIENCY

Results				Condition	Follow-up
Loss of Wt. (in Lbs.), Subjective and Objective Changes at End of		Total Time Loss			
One Month	Two Months	Mo.	Lb.		
-15 Mns. x 2, no dysm. No Pre T	-11 Slight dysm. No headache. Stronger and alert.	6	23	Symptomless. "Now able to work."	Did not return for check up. One year later wt. 225, symptomless.
-16 Slight dysm. No Pre T Slight headache. Stronger and alert.	-9 Improved flow No dysm. Improvement continued.	7	50	Mns. q 29 x 4 Symptomless. BMR +6. Pulse 80.	Did not return.
-4 Mns. x 4 slight dysm., fewer headaches stronger and alert.	-0 Symptomless.	2	4	Symptomless. BMR +6. Pulse 5	Total regression in 2 months. Four months treatment followed by 3 years without symptoms.
-0 Mns. x 2, no dysm. Fewer headaches.	-0 q 30 x 3. Slight dysm. Stronger and alert.	7	0	Mns. q 30 x 4. Symptomless. Hirsutism appreciably improved.	Did not return for two years. Gained 10 lbs. No hirsutism.
-13 Mns. x 2, improved flow, no dysm. Fewer headaches. No precordial pain.	-14 Improvement continued. Blood pressure 164/100.	7	53	Poor cooperation Mns. q 30 x 4 symptomless. BMR +6, pulse 72. B. P 158/96.	Did not return for one year gained 30 lbs. with return of symptoms.
-12 Mns. x 5, slight dysm. Fewer headaches.	-7 No polydipsia. No polyphagia. Slight dysm. No headache.	3	43	Mns. symptomless no acne, BMR +2 pulse 72.	Gained weight and treatment resumed Follow-up two and one half years later weighed 135 lbs. symptomless.
-0 No dysm. First time since menarche.	-0 No dysm. No Pre T Left clinic.	2	0	Cooperation poor Slight improvement of acne.	Insufficient treatment left clinic; regression immediate.
-3 Less dysm. Fewer headaches. Less dyspnea.	-10 Mns. x 4. No dysm. No dyspnea.	6	16	Symptomless. Pulse 84. Hirsutism unchanged.	No change in hirsutism. Remained well up to 3 months. Did not return.
-13 Less dysm. Less dyspnea.	-13 Improvement continued. Stronger	6	44	Symptomless.	Mns. normal, no gain or return of symptoms up to three months.
-0 Very slight dysm. (First time in 15 yr.). No premenstrual spotting.	-7 Symptomless.	3	7	Symptomless. BMR +3.	Pregnancy 6 months later Live child at term symptomless and no gain up to 1 yr. postpartum.
-12 Slight dysm. Fewer headaches. More alert.	-14 Mns. x 4 No dysm. No headache. Sleeps well.	4	47	School work improved. Symptomless.	Well with no gain of weight up to two years.

TABLE 3—AMENORRHEA ASSOCIATED WITH OBE

No.	Age, Status, Parity	Ht., Wt., in—lb	Pulse, B.M.R.	Past History	Present Menses	Present Symptoms
D 6701	36 M 0	62 213	60 +50	Mns. q 2-6 mo Never regular Dym.	Mns. for last few years q 5 mo	Headache. Somnolence. Mental sluggishness, hirsutism.
199857	26 M 2	62 203	72 +2	Menarche at 14—irregular x 7 7 mo ago Miscarriage.	Amnr Mns. q 6 mo	Fatigability Somnolence. Precordial pains. Gaining weight rapidly
B 0512	32 M 4	62 207	70 +8	Menarche at 11 q 34 x 8 Married—15 Wt 135 pregnant—16, wt at 23 165 lbs.	Amnr 3 mo Usually is irregular—6- 11 wks Dysmn	Headache. Somnolence. Mental sluggishness, insomnia, Polydipsia
A 10911	32 M 0	57 219	72 +20	Menarche at 13 q 28—5 yrs q 6 mo 2 yrs. Wt. 135 at marriage, 10 yrs. ago.*	Amnr Mns. a ' watery discharge once a year for 8 yrs. Sterility	Headache. Fatigability Discomforting obesity of thighs and abdomen
C 5538	13 S	60 167	75 +19	No menarche	No sign of epiphyseal closure in hands	Headache. Fatigability Mental sluggishness gain ing weight rapidly
D 12321	26 S	62 227	100 +22	Menarche at 16 Mns. once a year since.	Last menses occurred few days ago	Headache Mental sluggishness, somnolence. Coarse facial hirsutism
C 8143	26 M 2	62½ 245	78 +18	Menarche at 13 q 28 for 'few yrs. Amnr 1 yr Then regular	Amnr for 8 mo pre- ceded by very scant Mns.	Headache. Somnolence.
D 5404	25 M 0	59 162	90 +5	Menarche at 13 q 31 x 4	Amnr preceded by in- termittent spotting Sterility	Headache. Fatigability Somnolence. Precordial pain.
E 6401	14 S	63 231		No menarche.	Epiphyses of hand united. Lower radius and ulnar ep partial union. No pubic or axillary hair	Headache. Fatigability Dyspnea. Precordial pain Nocturia.
B 15769	12½ S	60½ 198	75 +16	Menarche 6 mo ago Mns. 3 times, dym., Pre T	Amnr 3 mo	Headache. Somnolence. Polydipsia. Polyphagia. Mental sluggishness.
C 13867	34 M 0	60 209	70 ?	Menarche at 10 q 28 x 7 irregular since marriage. Wt. 100 at 20 yrs.	Amnr since gallbladder operation 2 yrs. ago	Loss of libido. Gaining wt. rapidly (60 lbs. in 2 yrs.)
E 6537	14 S	62 161	66 -9	Menarche at 12 irregular from 3 wks. to 6 mo	Amnr Hand epiphyses not united	Mental sluggishness, somnolence. Severe headache. Gaining weight rapidly
A 12979	38 M 2	66½ 254	70 -1	Two children by former marriage. Now sterile	Amnr 6 mo Pregnant mare serum hormone with no change in signs or symptoms.	Headache Precordial pain. Fatigability Somnolence.

Mns. Pertaining to menstruation

Dym. Dysmenorrhea.

Amnr Amenorrhea.

Pre T Premenstrual Tension.

* Thyroid therapy with loss of 29 lbs. no change in menses or symptomatology

SITY AND SYMPTOMS OF PITUITARY DEFICIENCY

Results				Condition	Follow-up
Loss of Wt. (in Lbs.), Subjective and Objective Changes at End of		Total Time Loss			
One Month	Two Months	Mo.	Lb.		
-12 Mns. in 30 days. No headache. Very sluggish.	-11 Mns. in 35 days. Feels a little better.	7	45	Now able to work, pulse still slow (60) BMR +3, Mns. q 30 symptomless.	Up to 2 years, pulse remained slow tendency to remain sluggish, and regain weight. E.K.G. neg.
-13 Mns. after 6 wks. stronger and alert, no precordial pain.	-13 Mns. in 35 days. Improvement continued.	9 in 1 1/4 yrs.	63	Very good.	Up to two years no change.
-16 Mns. in 35 days. No Dysm., no headache. Stronger and alert.	-8 Mns. in 35 days. Improvement continued.	8	23	In spite of poor cooperation, condition good.	Did not return. One year later original weight and symptoms.
-13 Continual subjective complaints.	-12 Mns. in 9 wks. repeated in 30 days. Ovulation pain (?)	14	42	Amn. followed the two reported menses; at end of treatment found to be 8 months pregnant. Delivered of live normal child and was not seen again. Investigation revealed that she regained all weight in 2 years postpartum but did not return.	
-12 Slight headache. Stronger and alert.	-10 Mns. in 6 wks. No headache. Improvement continued.	5	27	Good. Mns. regular	Up to two mo. well. Did not return. 15 mo. later gained 60 lbs., Mns. symptomless.
- No headache. Stronger and alert.	-10 Mns. in 6 wks. (first time in less than 1 yr.)	7	39	Mns. q 33. Hirsutism appreciably improved.	Further treatment with no loss of weight. Mns. symptomless to 16 mo. Hirsutism cured.
-10 Mns. in 3 weeks. No headache	-9 Mns. in 30 days x 4 stronger and alert.	2	19	Left clinic.	Did not return.
-2 Mns. x 5 (first good flow in 6 mo.) No precordial pain.	-16 Mns. in 30 days. Improvement continued.	2	12	Good.	Up to 2 mo. lost 18 lbs. At third month, pregnant, miscarriage in third month.
-12 Mns. in 3 wks. no headache, nocturia, precordial pain, or dyspnea.	-0 Mns. in 30 days. No precordial pain. Stronger and alert.	9	45	Cooperation poor. Mns. symptomless.	Up to 3 mo. gained 12 lbs. Did not return.
-8 Stronger and alert.	-5 Mns. in 6 wks. School work improved.	12	30	Mns. symptomless. Good.	At 2 mo., symptomless and regular Mns., no gain in weight. Did not return.
-13 Much better increased libido.	-2 Mns. in 7 wks. (first in 2 yrs.)	6	33	Treatment irregular due to poor cooperation. Mns. irregular.	Did not return.
-1 Mns. x 4. No headache. Stronger and alert.	-4 Mns. q 30. School work improved.	3	5	Mns. symptomless.	Did not return regularly. Two years later gain in weight, Mns. irregular.
-0 No headache. No precordial pain. Stronger.	-0 Mns. in 6 wks. (first in 6 mo.)	3	0	No loss of weight. Feels much better.	Did not return. One yr. later miscarriage. Loss of 22 lbs. 2 yrs. later, pregnancy to term.

TABLE 4—HYPOMENORRHEA AND OLIGOMENORRHEA ASSOCIATION

No.	Age, Status, Parity	Ht., Wt., in.—lb	Pulse, B.M.R.	Past History	Present Menses	Present Symptoms
E 2909	39 M 3	62 180	75 +4	Menarche at 16 q 30 x 5	q 28-32 x 2 Hypm. and Pre T	Headache Somnolence. Emotional instability Dyspnea. Backache.
B 7867	34 M 8	60 202	110 +27	Menarche at 11, q 28 x 3, Dysm. to first pregnan- cy thin at 14 137 at 17	Irregular Hypm. for last 4 yrs Miscarriage 4 mo ago	Headache. Fatigability Dyspnea.
B 11482	28 M 1	56 3 173	80 +2	Menarche at 13, q 30 x 4, normal mns. (?) under M D a care only to marriage.	Scant dribbles since child birth 4 yrs. ago	Headache Fatigability Gaining wt. rapidly
B 3796	14 S	68 220	70 +6	Menarche at 10 irregular Mns for 6 mo Irregular spotting since.	Scant irregular staining	Polydipsia. Polyphagia. Gaining wt. rapidly
199914	29 M 2	66 330	75 -17	Menarche at 12	Irregular episodes of dribbling for weeks at a time for last 5 yrs.*	Headache. Fatigability Polydipsia. Polyphagia. Dyspnea.
C 7615	34 M 4	64 209	72 ?	Menarche at 11 q 26 x 5 At 17 wt. 118 At 19, 138 lbs.	Hypm, Mns. less than 2 days.	Fatigability Somnolence. Emotional instability Polydipsia. Polyphagia. Loss of libido
D 14121	30 M 2	61 168	75 +6	Menarche at 13 q 28 x 4	For last 2 yrs. hypm.†	Headache. Somnolence Emotional instability Gaining wt. rapidly Polydipsia. Polyphagia. Loss of libido.
C 17577	31 S	59 164	95 +9	Menarche at 12 q 30 x 3	Hypm. for last 5 years	Fatigability Somnolence. Emotional instability Hirsutism
S M	29 M 2	66 148	60 -21	Menarche at 12 q 28 x 5 Dysm to marriage	Mns x 1 Hypm. Pre T	Headache. Fatigability Emotional instability
F M	33 M 2	59 157	72 -6	Menarche at 13 q 28 x 3 with dysm. and nausea.	Hypm	Headache. Fatigability Emotional instability
W R.	32 M 2	59.5 185	70 -1	Menarche at 13 q 28 x 5	Hypm x 1 for last 6 months.	Headache. Polydipsia Polyphagia Backache. Gaining wt rapidly
D 7173	15	64 174	65 -10	Menarche at 11 q 28 x 3	Hypm. x 2 Pre T ‡	Headache. Mental sluggishness.
B 13649	39 M 8	60 5 230	68 +19	Menarche at 14 q 28 x 3	Hypm. x 1 Pre T ‡	Headache. Polydipsia. Polyphagia. Dyspnea.

TED WITH OBESITY AND SYMPTOMS OF PITUITARY DEFICIENCY

Results		Total Time Loss		Condition	Follow-up
Loss of Wt. (In Lbs.) Subjective and Objective Changes at End of		Mo.	Lb.		
One Month	Two Months				
-11 Improved menstrual flow; no headache. No dyspnea.	-8 Mns. in 30 days. Slight Pre T. No headache. Stronger and alert.	7	33	Very good. Mns. q 30 x 2. Symptomless.	Follow-up to one year: remained well and Mns. normal. Was treated previously as "Early menopause."
-10 Pulse 76 stronger and alert; no headache or dyspnea.	-2 Mns. 3 days (first time in years) Left clinic	2	12	Cooperation poor fair	Treated on and off irregularly due to poor cooperation. Left clinic to return one year later Wt. 242.
-7 Mns. 4 days, no headache, stronger and alert.	-11 Improvement continued. No headache.	5	31	Good.	Did not return for check up. One year later returned after miscarriage; gained 25 lbs. and onset of symptoms.
-6 Improved mns. flow	-0 Mns. 5 days. Left clinic.	2	3	Cooperation very poor Left clinic.	Treatment was impossible due to lack of cooperation. One year later after removal of an ovarian cyst, weighed 255.
-12 Fewer headaches. No dyspnea stronger and alert.	-3 Mns. 3 days. Improvement continued.	6	23	Good. Is now able to work	Did not return for check up gained 21 lbs. in 6 mos., symptomless refused further treatment. After 15 mos., gained 5 lbs. with return of symptoms.
-13 Mns. 5 days. Stronger and alert.	-11 Mns. 3 days. No emotional instability	4	35	Very good symptomless.	Remained well for three months, did not return for further check-up
-4 Improved menstrual flow Fewer headaches. Stronger and alert.	-7 Improvement continued.	4	13	Mns. symptomless general condition—no complaints.	Lost one pound in following month. Never returned to clinic.
-0 Mns. 4 days. Stronger and alert.	-10 Improvement continued.	6	29	Stabilization of an agitated neuroticism. Slight improvement of heart m.	Improvement continued up to one year. Hirsutism appreciably improved.
-0 Mns. 3 days. Less Pre T. Fewer headaches.	-3 Improved Mns. flow no headache.	3	3	Good. B.M.R. -12.	No gain in weight or return of symptoms up to 2 years
-0 No headache. Less emotional instability	Did not return to clinic.	1	0	Loss of fat deposits. Did not return to clinic.	Did not return.
-7 No headache. No backache. Mns. 3 days.	-8 Mns. 3 days. Improvement continued.	3	23	Very good. Symptomless.	Did not return for 3 years. Recurrence of weight and symptoms. Treated again with good results.
-17 Improved flow No headache or Pre T	-13 Mns. 3 days. Stronger and alert	4	33	Good.	Up to eight months, lost 8 more lbs. and remained symptomless.
-12 Improved flow No dyspnea. Fewer headaches.	-3 No headache. No Pre T. Improvement continued.	12	37	Symptomless. Mns. normal. BMR +5. Pulse 60.	Up to eight months 6 more pounds lost and remained symptomless.

TABLE 4—HYPOMENORRHEA AND OLIGOMENORRHEA ASSOCIATED

No.	Age, Status, Parity	Ht., Wt., in.—lb.	Pulse, B.M.R.	Past History	Present Menses	Present Symptoms
D 0437	30 M 3	62 189	78 —2	Menarche at 14, q 28 x 4.	Hypm q 25 x 3 Pre T	Fatigability Insomnia. Gaining wt. rapidly
E 7858	17 S	60.5 153	80 —14	Menarche at 11, q 28 x 3	2 Hypm., Olgm (q 2 mo) Faints with Mns Pre T	Acne. Hirsutism (extensive facial)
S F	18 S	62 163	60 —30	Menarche at 14 q 28 x 7	q 2-3 mo x 1 Hypm., Olgm., Pre T for last yr	Fatigability Somnolence. Acne, gaining wt. rapidly
H K.	26 M 0	63 148	62 —23	Menarche at 12.	Mns. gradually diminish- ing to scant dribble Pre T	Headache. Fatigability Mental sluggishness. Hirsutism. Gaining wt. rapidly
F T	36 M 0	61 146	75 —13	Menarche at 13 q 28 x 5 2 yrs. ago Amnr 4 mo	q 6-8 wks. Hypm. Sterility	Gaining wt. rapidly* loss of libido
A 7480	39 M 2	60 191	90 +3	?	Hypm. x 1 Pre T	Headache. Somnolence. Polydipsia. Gaining wt. rapidly
188407	35 M 12	61 188	80 ?	Menarche at 12	Hypm. Olgm., Pre T irregular by wks. to months.	Headache. Fatigability Somnolence. Insomnia. Emotional instability

Mns. Pertaining to menstruation.

Dysm Dysmenorrhea.

Hypm. Hypomenorrhea.

Olgm. Oligomenorrhea.

Amnr Amenorrhea.

Pre T Premenstrual tension.

* Thyroid therapy for two years with no change in weight, symptoms, or character of menses.

† Thyroid therapy 50 lbs loss, no other effects.

‡ Loss of 10 lbs. with diet no other effects.

§ Thyroid therapy for five years no loss of weight or other changes.

cluded in the series reported herein. When other blood studies could be done (fasting sugar, sugar tolerance estimations, complete blood count, cholesterol, uric acid and blood nitrogen determinations) they were often diagnostically disappointing. Sugar tolerance, cholesterol and uric acid estimations tended to be high, while relative lymphocytosis was frequently noted.

THERAPY

Treatment consisted of diet, desiccated thyroid by mouth, and anterior lobe pituitary extract by injection. To avoid possible confusion

WITH OBESITY AND SYMPTOMS OF PITUITARY DEFICIENCY (*Continued*)

Results					Follow-up
Loss of Wt. (in Lbs.) Subjective and Objective Changes at End of		Total Time Loss		Condition	
One Month	Two Months	Mo.	Lb.		
-7 Improved flow Stronger and alert, no Pre T	-8 Mns. in 23 days x 4 im- provement continued.	8	15	Mns. q 30 x 4 symptom- less.	Did not return.
-8 Mns. in 20 days. Improved flow No fainting spell.	-9 Mns. 6 days, symptom- less.	6	25	Acne, improved. Hirsutism improved. Mns. symptomless.	Improvement continued for one year Acne and hirsutism still under treatment.
-3 Mns. in 40 days x 6 no Pre T Stronger and alert.	-4 Mns. in 23 days.	2	7	Felt fine, left clinic for summer	Returned in 3 mo. with total recurrence. Treated 3 mo. with improvement and remained well up to two years.
-3 Improved flow Less Pre T No headache.	-2 Mns. 4 days. No Pre T	2	5	Loss of fat deposits. Good.	Hirsutism unchanged. Did not return.
-1 Improved flow Increased libido.	-3 Mns. in 20 days x 2.	4	12	Changed appearance, animated.	Up to one year symptom- less with no gain in weight. Mns. regular but tend to Hypn.
-9 Mns. in 21 days x 2, no headache, stronger and alert.	-7 Mns. 4 days. No headache. No Pre T	2	20	Symptomless.	Did not return for 1 yr Gained 31 lbs., Mns. q 31 x 2, symptoms returned.
-12 Mns. in 30 days, scant, no headache; less in- somnia.	-10 Mns. in 30 days, scant, no Pre T	8	43	Stronger and alert, symptomless, Mns. normalized.	Lost 12 lbs. in first 2 mo. and remained symptom- less. Did not return for 8 months, gained 42 lbs., headache and Hypn.

when evaluating therapy and because no individual symptom in any of our patients in this series was considered important enough to merit it, no other therapeutic measures were taken than those about to be described

Diet—A diet high in protein moderate in carbohydrate and low in fat content was prescribed for all patients in this series. However, strict adherence to a diet totalling 900 calories could hardly be expected from clinic patients. Regular eating, no eating between meals, and limitation of the salt and water intake (where indicated) were stressed. The directions were as simple as possible and an attempt was

TABLE 5—HYPERMENORRHEA AND POLYMENORRHEA ASSOCIATED WITH

No	Age, Status, Parity	Ht., Wt., in—lb	Pulse, B M.R.	Past History	Present Menses	Present Symptoms
D 9602	31 M 2	64 222	70 +14	Menarche at 11 irregular Mns. off and on up to first pregnancy	q 3 wks. Dysm. Pre T Diarrhea. Polym.	Headache. Fatigability Emotional instability 50 lbs. gained in 1 yr
B 5603	31 M 2	60 168	80 +3	Married at 16 weighed 99 lbs.	q 3 wks. x 7 Polym. and Hyprn. Pre T Duration 2 yrs.	Fatigability Somnolence. Emotional instability Polydipsia. Nocturia. Acne.
A. C	33 M 2	65 180	78 -6	Menarche at 14 regular but always had heavy flow	q 25 x 7 Polym. and Hyprn. Pre T	Headache. Emotional instability Loss of libido
F B	36 M 0	64 153	70 -2	Menarche at 15 every 24 days x 4	q 24 x 8 Polym. and hyprn. Pre T	Headache Emotional instability 15 lbs gained in 2 mo
C 10840	26 M 0	66.5 291	82 -1	Menarche at 13 Mns. every 6 mo at 14 q 30 days. Grew rapidly— span 70 in.	q 2 wks Polym and hyprn. for last 4 mo Gained 150 lbs since marriage one yr ago	Headache. Fatigability Polydipsia. Nocturia.
E 2645	29 S	53 164	85 +18	Menarche at 11, q 18 days x 4 Polio-paralytic 20 *	q 14-20 days. Polym., Dysm., Pre T	Headache. Emotional instability
D 14312	13.5 S	61 151	75 -1	Menarche at 11 q 28 x 7 Pre T and Hyprn.	q 28 x 7 Hyprn Pre T Leukorrhea.	Polydipsia. Polyphagia. Ununited epiphyses in hand.
108617	27 S	63 183	78 -6	Menarche at 13, q 30 x 4 at 16 q 21	q 21 x 4 Polym and Hyprn Pre T	Headache. Dyspnea. Mental sluggishness.

Mns. Pertaining to menstruation.

Dysm. Dysmenorrhea.

Hyprn. Hypermenorrhea.

Polym. Polymenorrhea.

Pre T. Premenstrual Tension

* Lost 20 lbs. on diet without change in symptomatology or character of menses.

made to "teach" proper eating, a measure that would have to be maintained even when the patient was "cured" if regression was to be prevented

Medication—*Desiccated Thyroid*—One gram of desiccated thyroid

ATED WITH OBESITY AND SYMPTOMS OF PITUITARY DEFICIENCY

Results				Follow-up	
Loss of Wt. (in Lbs.), Subjective and Objective Changes at End of		Total Time Lost			Condition
One Month	Two Months	Mo.	Lb.		
-12 Mns. in 30 days. Cooperation poor	-8 Mns. in 30 days. No Dysm. No diarrhea, headaches or Pre T	6	30	Treatment irregular due to poor cooperation. Symptomless. Pulse 72 BMR +6.	Did not return.
-12 Mns. in 30 days. Bleed- ing less five days. No nocturia or Pre T Stronger and alert.	-7 Mns. in 30 days, symp- tomless no nocturia. Improvement contin- ued, left clinic.	2	70	Fair	Returned in three months symptomless but gained 15 lbs. Symptoms re- turned in 5 months. Treated again—immedi- ate improvement.
-0 Mns. in 23 x 5. Less bleeding. No Pre T	-5 Mns. in 24 x 4. Stronger and alert, in- crease of Mido. No headaches.	2	5	Good.	For last three years, one month treatment given every eight months this controls tendency to- wards regression.
-8 Mns. in 26 x 5. Fewer headaches. No Pre T Stronger and alert.	-5 Mns. in 26 days. Diminished flow No headaches.	2	13	Very good.	Regular check-ups for two years. Remained well.
-0 Mns. in 30. Fewer headaches. Less polydipsia. No nocturia.	-11 Mns. in 30 days. Diminished flow No polydipsia. Stronger and alert.	6	33	Fair—treatment irregu- lar during 8 months; tendency towards to- tal regression without treatment.	Treated on and off for 18 months. Cooperation poor after slight improvement takes place. Two years later pregnant—severe nausea throughout preg- nancy interrupted for di- agnosed anencephalic monster (seventh month)
-8 Mns. in 23. Stronger and alert.	-0 Mns. in 26 days. No Dysm. or Pre T Less cranky	4	13	Menstrual interval re- mained 26 days. Oth- erwise symptomless. "Gets about better"	Did not return.
-11 Mns. x 4 days. Bright Pre T "Better natured."	-1 Mns. x 4 No Pre T No leukorrhea.	3	12	Fair after 3 months. Left clinic.	Returned 8 months later, gained 12 lbs., "bloated," sluggish, somnolent, and some menses irregular. Two months treatment— symptomless and loss of weight.
-11 Mns. in 26 days. Bright Pre T No dyspnea.	-6 Mns. in 22 days. No Pre T Stronger and alert.	3	33	Good.	Did not return for 18 months. Married and gained 50 lbs. in 6 mo. but remained symptomless.

daily by mouth was prescribed In the presence of an unchanged pulse rate or a pulse rate below 90 the dosage was increased by one grain every two weeks until an elevated pulse rate or subjective symp

toms indicated that the point of tolerance had been reached. The metabolism of patients with an initially high basal metabolic rate was

TABLE 6—ASSOCIATION OF SYMPTOMS WITH MENSTRUAL DISORDERS IN FIFTY-TWO FEMALE OBESE PATIENTS

Symptom	Dysmenorrhea (11 Cases)		Amenorrhea (13 Cases)		Oligo- and Hypo- menorrhea (20 Cases)		Hyper- and Poly- menorrhea (8 Cases)	
Headache	10	90% of total in this group	11	83%	18	90%	8	100%
Fatigability	6	54%	5	37%	15	75%	3	37.5%
Somnolence	3	27%	9	70%	10	50%	1	12.5%
Emotional instability	2	18%	0		7	35%	5	62.5%
Precordial pain	1	9%	4	30%	1	5%	0	
Backache	0		1	7.5%	2	10%	0	
Nocturia	1	9%	1	7.5%	1	5%	2	25%
Polydipsia and poly- phagia	3	27%	2	15%	8	40%	4	50%
Loss of libido	0		1	7.5%	3	15%	1	12.5%
Hirsutism	2	18%	2	15%	4	20%	0	0
Acne	2	18%	0		2	10%	3	37.5%
Insomnia	2	18%	1	7.5%	3	15%	1	12.5%
Premenstrual tension	5	45%	0		9	45%	7	87.5%
Mental sluggishness	3	27%	6	45%	3	15%	3	37.5%
Dyspnea	2	18%	1	7.5%	4	20%	1	12.5%

estimated regularly, close watch being kept meanwhile for suggestive subjective symptoms. Patients reported so frequently, however, that they were "less nervous," and the pulse rate was so often found to

TABLE 7—BASAL METABOLIC RATE VARIATIONS IN PATIENTS WITH OBESITY ASSOCIATED WITH OVARIAN DYSFUNCTION

Basal Metabolic Rate	No. of Patients in Engelbach's Series	Our Series* No. of Patients
+21 or over	28	7
+11 to +20	33	9
+10 to -10	97	25
-11 to -20	72	5
-21 or lower	34	3
Total Patients	264	49†

* Females only

† In three patients, adequate basal metabolism determinations were unobtainable.

have been reduced after treatment was commenced, that eventually an improved appearance, fewer symptoms and a more normal pulse rate became our criteria for increasing dosage.

Pituitary Extract—A water soluble unfractionated extract of the anterior lobe of the pituitary* was used. There is no doubt that a widespread skepticism exists concerning the efficacy of nonfractionated extracts of the anterior lobe of the pituitary (Indeed, the acceptability of our clinical results may be questioned on the ground that the extract cannot be assayed in units of potentialities)

However, anterior lobe pituitary extract therapy dates back to Cushing. In his work on the pituitary body, published in 1912,⁵ he described a woman who, at the age of 40 showed signs of progeria uninfluenced by desiccated thyroid. Cushing then treated her with anterior lobe extract, as a result of which "she changed from her former drowsy, inert mental condition to one of lively buoyancy in which she began for the first time to show interest in her surroundings. In one month her menses appeared after three years of amenorrhea." Discontinuance of medication brought a return of symptoms followed by renewed well being upon restoration to medication.

Before this (1909), Cushing stated⁶ "We can even now with reasonable certainty anticipate the results of anterior lobe administration for the adiposity associated with conditions of hypopituitarism and it is probable that of the many cases of adiposity of diverse origin which have benefited in the past by thyroid administration have been so benefited in consequence of the indirect awakening of activity in the hypophysis."

In the bibliography will be found other instances of successful therapy with anterior lobe extract. The present status of pituitary hormone evaluation depends on the extraction of specific factors and their assayed effects on the animal. Yet not one of these carefully assayed pituitary hormones has produced consistent therapeutic effects in man. Some have elicited alterations in certain physical signs but in no instances was generally improved physiology reported. In obese children especially where synchronous development is desirable the use of specific hormones—either an efficient gonadotrope or the gonadal hormones themselves—can at most alter an endocrine imbalance not correct it.

Whenever the patient to be treated was extremely obese or if she exhibited "puffiness" or a bloated appearance, we added 0.3 cc. of posterior lobe extract (*obstetrical pituitrin*) which was increased by 0.1 cc. at each dose until tolerance (intestinal rumbling or cramps) was reached. If the patient could not maintain at least 0.5 cc., obstetrical pituitrin was discontinued.

If hypertension and/or precordial pain accompanied the obesity all medication was given with great care, and increased cautiously.

* Most of the material used throughout this work and later was preparation "Water Soluble Extract Anterior Pituitary Substance" from the Armour Laboratories, Armour & Co., Chicago, Illinois.

RESULTS

Response to therapy has been evaluated on the basis of improvement or alteration in *every* phase of complaint. This is emphasized lest it be thought that the rationale of treatment was directed toward im-

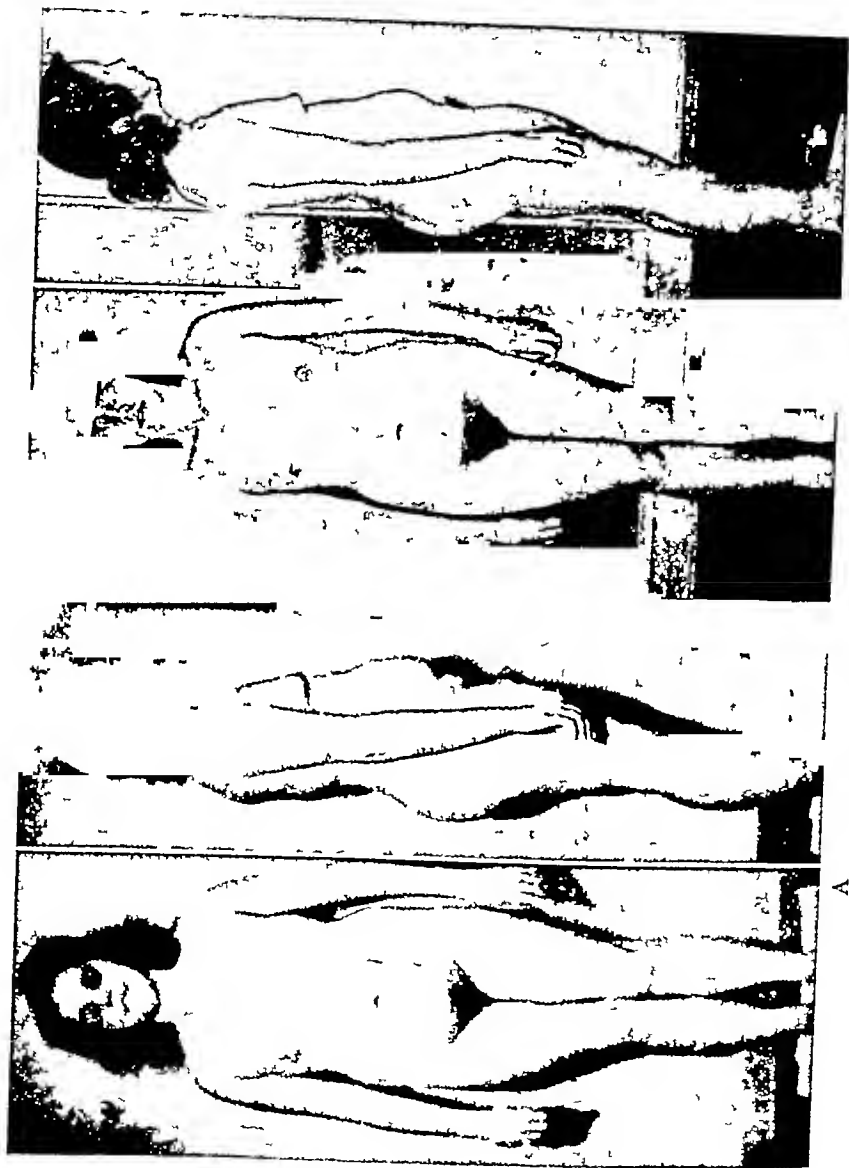


Fig 111 (Case D 12786, Table 2) —Severe dysmenorrhea and profuse flow, headaches, rapid increase in weight, acne. Aged 13, height 65.5 inches, weight 185 pounds. A At beginning of treatment B, Eight months later weight 142 pounds menses symptomless, flow normalized. Note diminution of fat deposits

proving isolated symptoms. To present all cases in detail would involve too lengthy delineation. Moreover, the patients varied greatly in physical signs and symptoms both as to number and degree so that results can only be generalized. However, each patient stands alone

as an interesting clinical experience and details are given as fully as possible in Tables 2 to 5 inclusive

As a rule, improvement was noted within one or two weeks. By the end of the third week, no suspicion of a headache remained. So consistently did headaches disappear that any degree of head discomfort was considered proof that other disease was probable. Acne responded to general improvement of ovarian function. This applies to the premenstrual type as well as to the generalized type. It must be mentioned that a bullous or pustular lesion indicates local treatment before trophic changes can be expected. Hirsutism, too, improved with betterment of ovarian function except in cases of long standing especially in those patients who had been subjected to a great deal of physical or chemical treatment.

General symptoms vanished within a month. Pointed questioning was avoided. The patients were simply asked to describe how they felt and it was noticed that they did not mention their former poignant complaints. At a later date, these complaints were investigated and found to be "gone."

Many patients lost a great deal of weight, chiefly in the first two months. No patient gained weight in some no weight was lost. Loss of weight *did not necessarily accompany* looseness of clothes or improvement in other phases of the complaint. Many patients were on "poor relief," which meant potatoes and bread instead of proteins and green vegetables. Phenomenal loss of fat deposits without a proportional loss of weight was noted also by Beck.¹⁰

Patients originally dishevelled and slovenly began to appear by the end of the third week with lipstick and hair-do. Many of those women who showed no appreciable loss of weight, reported that they "felt lighter." Relatives and friends and in the case of the younger patients, school reports confirmed the patient's improvement, by indicating disappearance of emotional instability, increased efficiency of endeavor, and a better accommodation to environment.

Considerable disappointment was felt with regard to follow up co-operation. Many patients left the clinic against advice as soon as they felt better only to return within a few months showing complete regression. Treated anew they improved again. But not every patient returned for a check up and such further treatment. In those patients who did cooperate properly it was found that, after normalization, short periods of treatment at determined intervals helped to maintain normalcy.

The length of treatment depended upon loss of weight and improvement in the patient's menstruation. Adequate treatment was inferred from changes during trial periods of rest from treatment. Actually the alterations that took place in the menstrual phenomena in a relatively short time were almost dramatic, especially so when patients with opposite extremes of bleeding reported changes toward

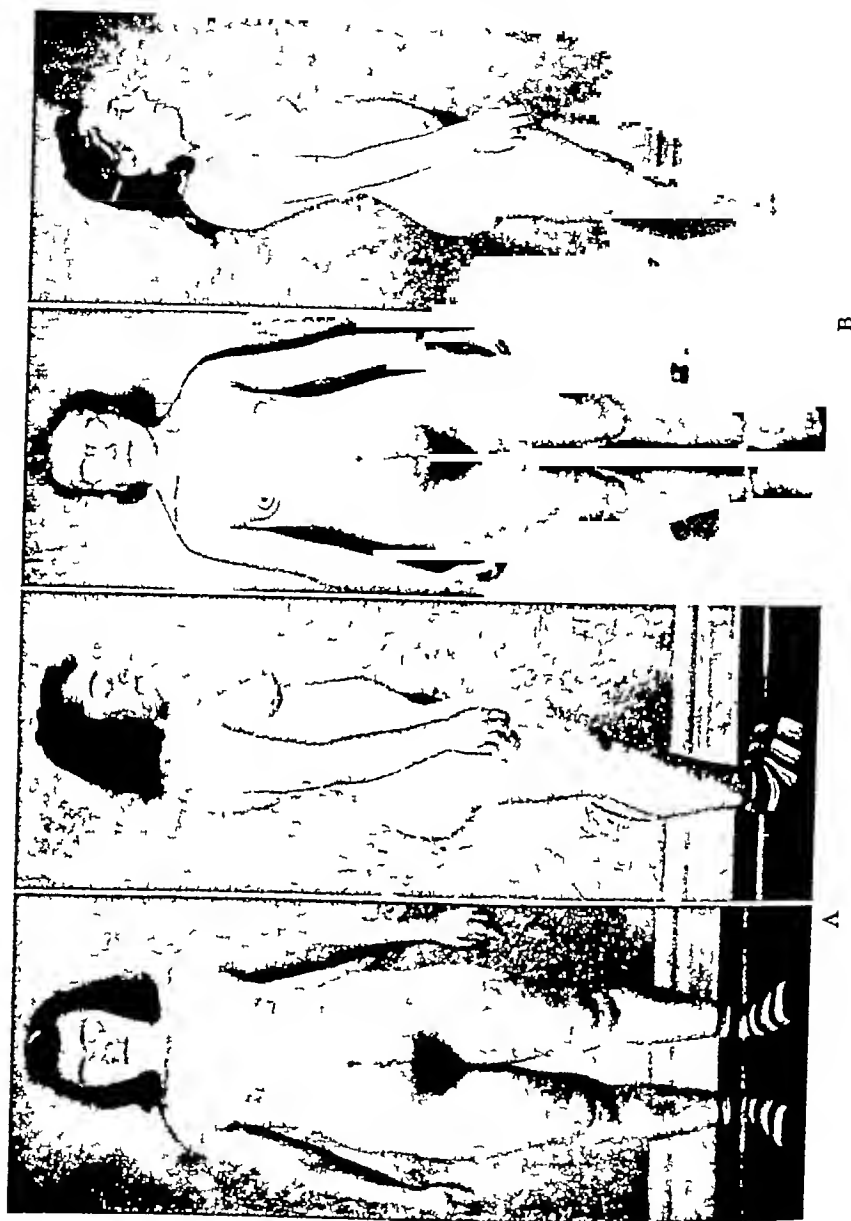


Fig 112 (Case E 7858, Table 4) —Oligomenorrhea, hypomenorrhea, premenstrual tension, acne and hirsutism Fainted with menstruation every two months Aged 17, height 60 5 inches, weight 153 pounds A, Coarse features and fat deposits at beginning of treatment. B, After four months of treatment Weight 125 pounds Note disappearance of fat deposits and general improvement in features Menses normalized in six weeks (In two years following treatment, no weight was gained Menstruation remained normal Facial acne and hirsutism improved sufficiently to evaluate response to therapy The severe bullous and pustular lesions recurred intermittently, they were never quite controlled because of unavailability of local treatment and poor cooperation The hirsutism is definitely improved, however, in that recurrence of hair growth after removal by plucking is slower)

normalcy One patient was found to be pregnant while under treatment. She had previously menstruated once a year for eight years (A 10911, Table 3) With few exceptions, alterations in menstrual disturbances occurred *before* material loss of weight was noted

It was noticed, also, that after treatment was discontinued—that is, after a patient stopped coming to the clinic—a severe illness, surgical procedure or pregnancy tended to precipitate regression



Fig. 113 (W R., private patient, Table 4)—Hypomenorrhea. Treated for three months with loss of 22 pounds from initial weight of 185 pounds and general improvement. Two recurrences of obesity within three years A Appearance three years after original treatment showing recurrence of obesity B, After seven weeks of treatment. Weight 172 pounds Severe headaches and backaches gone. At the end of three months of treatment patient had lost an additional 20 pounds in weight.

In three cases the first injection of anterior lobe extract was followed within a few hours by a severe urticarial reaction, namely giant wheals with itching Treatment was discontinued and so none of these cases is included in this series that we are reporting

We have drawn no conclusions from patients whose treatment included posterior lobe extract (obstetrical pituitrin)

COMMENT

The premise was accepted that these patients were essentially cases of thyroiditis deficiency The symptoms as listed, together with obesity and menstrual disturbances varied little in detail from those attributed to pituitary deficiency by Cushing,⁵ Cushing and Goetsch,⁷ Jarlov,⁸ Engelbach,⁴ Pardee,⁹ Beck,¹⁰ Simmonds (quoted by Beck), Pratt,¹¹ Timme,¹² Calder,¹³ Rowe and Lawrence,¹⁴ Goldzieher¹ and others Timme claimed that any "one" of them may point to

pituitary deficiency, but when several are found in the same patient, "the presumption is strong that such a deficiency exists"^{12, a} The association of pituitary deficiency with diminished thyroid activity not only has been pointed out by Cushing,⁵ Smith,^{15, 16} and Moore and his co-workers,¹⁷ but its therapeutic synergy has been specifically demonstrated by Jacobsen and Cramer¹⁸ Indeed, in many of the patients of our series and in a number treated since in clinic and private practice, there were several instances in which a reported low basal metabolic rate had led to thyroid therapy with no improvement in complaints until pituitary extract was added to the medication Oft-encountered high metabolic rates, especially when accompanied by emotional instability, had even led to thyroidectomy In fact, Du Bois¹⁹ claims that a "slavish adherence to the basal metabolic rate as an index of diagnosis may lead the physician into trouble, first, because the test does not always give the true basal metabolism, and second, because even the true metabolism does not always indicate the correct diagnosis"

The results as depicted are neither novel nor original Similar results have been obtained and reported by many^{1, 4, 5, 9, 10, 12, 13, 18} Truly it merits repetition over and over again that a gland so small as the pituitary can exhibit so many manifestations of its function and so many complicating signs of its deficiency What is more remarkable, but at the same time to be expected, is that its more obvious and isolated functional exhibitions become more complex as we go up the animal scale, until by the time the human organism is reached, interrelationships and interactions becloud the identity and limit the identification of specific effectors in that small insular organ within the confines of the sella turcica of the skull To clarify the variabilities met in "obese thyropituitary deficiency," we must again scan the effects of hypophysectomy as shown by Smith,¹⁵ and the effects of hibernation illustrated by Moore and associates¹⁷ No matter what the effects of hypophysectomy are, they proceed more rapidly in the animal than in man when due to underfunctioning in the latter Besides, in man, resulting phenomena must be followed sooner or later by resultant phenomena as the function of other tissues and organs fails, according to sites of predilection and individual susceptibilities Signs and symptoms produced by offending organisms which bring about disease can adhere to clear-cut patterns But signs and symptoms produced by organs whose activities exist as potential energies, kept in check and unreleased because of insufficient extrinsic influence, must vary according to age at the time of onset, duration and intensity of that deficiency The direct effect of the glands of internal secretion upon the autonomic nervous system is well established When there is an imbalance in the latter subjective disturbances can run berserk, to say the least, producing an excessive strain on the compensatory mechanisms of the body²⁰

In the relatively recent laboratory experiments on animals, biochemical reactions may explain the coexistence of symptoms that appear to be unrelated. The work of Long,¹ Lee,² Cuthbertson Webster and Young,²³ Soskins and co workers,²⁴ and Paschke²⁵ bring more specifically to light the metabolic processes which explain the utilization, assimilation and storage of food. Proteins and carbohydrates are stored especially in the muscles which are then called upon as energy sources and again replenished. In hypophysectomized animals, the food stores are depleted, due to faulty replenishment. It has been brought out further that a hypophysectomized animal cannot call upon fats and proteins as noncarbohydrate sources of blood sugar, and death takes place immediately if the animal is starved. Jarlov⁶ suggested that the feeling of hunger is regulated and controlled by a feeling of satiation at the proper time. Obesity must be exogenous, but polyphagia may be the physiological response to just such an absent feeling of satiation as could be expected from an unmaintained blood sugar level and depleted protein and carbohydrate stores. Fats are totally inert under these circumstances. What better cause could be offered for the deposits of fat? And may not a "fat" individual hide a relative cachexia? Cause enough in these physiological findings for fatigability, weak spells, and any part of the chain of symptoms characterizing hypoglycemia.

Salt and water retention with attendant renal vagaries, in spite of many theories involving neighboring areas of the brain are attributed by Richter⁶ to the anterior lobe of the pituitary through its general control of metabolism, rather than to a separate specific hormone.

Variableness in the Menstrual Phenomena—Ovaries are not self-sustaining structures.¹⁶ Under the influence of the anterior lobe they begin early in life to develop follicles.²⁷ The estrogen produced before puberty can effect the endometrium only in a developmental sense—to mature it for its later function. After puberty, when and if the pituitary influence fails the mature endometrium reacts differently to the irregularity of an unbalanced production of ovarian hormones with faulty timing. As Engle²⁸ observes "Until a given cell has reached its intrinsic degree of maturity, no extrinsic factor becomes operative." No matter what the titer of ovarian hormone may be regardless of how the older endometrium reacts any type of bleeding or its absence is possible. Novak²⁹ has not only demonstrated the presence of anovulatory bleeding in instances of apparently normal menstruation but he claims that bleeding does not necessarily parallel endometrial growth and that the bleeding "spill" may occur at any level.³⁰ Others^{31 32} hold similar views.

Types of abnormal menstruation in the presence of obesity and hypopituitarism are important only as they coexist with other symptoms and except in emergencies merit no specific therapy. The endocrine responsibility must be considered pituitary hypofunction.³²

Fluhmann³⁴ states "Menstrual abnormal phenomena are symptoms and not disease entities, but the overwhelming majority of clinicians do not approach the subject that way"

The role of the pituitary gland is admittedly complex. Its effects are prominent, specific, varied and widespread. *Resulting* phenomena must be differentiated from *resultant* phenomena. The origin of the disturbance must be traced back to the point from which all interrelationships between interacting organs and glands have deviated from their synchronous precision.

CONCLUSION

Obese thyropituitary deficiency is characterized by a uniform triad of signs and symptoms which include obesity, menstrual disturbances (hypogonadism) and symptoms of pituitary deficiency. Its obesity may be slight, its genital involvement may be difficult to evaluate, its associated symptoms may be masked by degree, by temperament, by the compensatory mechanisms of the body, and by a total lack of uniformity.

The uniformity and predictability of response to therapy with thyroid and anterior lobe extract in all three phases of the triad make the assumption reasonable that, in spite of the variabilities encountered, a distinct clinical entity exists.

The patients chosen for report were selected because they illustrate gonadotropic response (menstrual phenomena). Except for this demonstrability, similar results were obtained in males and females of all types and ages.

The degree of deficiency of the anterior lobe cannot be inferred from the severity of the symptoms or from the promptness of the therapeutic response. It may be inferred from the rapidity of regression after treatment is discontinued.

Individual signs and symptoms are important only as they coexist and in themselves cannot be expected to aid in diagnosis or differential diagnosis, nor can we, by their alteration, influence the general condition. This applies especially to patients whose endocrine imbalance progresses, leaving prominent stigmata of a former imbalance.

I have in this paper endeavored to demonstrate the favorable response to therapy, and not "cure," in the patients presented. The physiological balance of an individual is the sum total of all the interrelationships and interactivities of the organism. That balance can be neither too specifically analyzed nor can it be any more than relatively normal. Some patients seem to have been normalized. One can not predict the result of some future stress and strain. Some patients need repeated courses of treatment. Cushing⁶ found that "in the examination of 100 (pituitary) glands taken at random from autopsy material, histological alterations are common." Unfortunately, neither by

x ray nor by an evaluation of symptomatology can we even approach an estimation of histological damage

SUMMARY

Obese thyroid-pituitary deficiency is defined as a distinct category of hypopituitarism. Its signs and symptoms are established in a pathognomonic triad—obesity, menstrual disturbances (gonadal inadequacy), and signs and symptoms characteristic of an hypofunctioning pituitary gland.

Symptoms, as they are associated with each other, are stressed above the isolated symptom, as criteria of diagnosis and for choice of therapy.

Pathogenesis, diagnosis and the so-called symptoms of hypopituitarism are discussed, on the basis of patients herein described and the experience of eminent authorities, in both the clinic and the laboratory.

Therapy with desiccated thyroid and a water soluble extract of the anterior lobe of the pituitary body has produced uniform and predictable responses in a large series of patients.

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AN EPIDEMIC CAUSED BY A SULFADIAZINE-RESISTANT STRAIN OF GROUP A TYPE 17 STREPTOCOCCUS

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THE spread of communicable disease by the migration of individuals or of groups has long been recognized. In wartime, the concentration of populations at army camps and increased travel commonly result in the development and dissemination of epidemic strains of various pathogenic bacteria.

Because the transfer of communicable diseases between Army Air Forces installations by troop movements was a frequent occurrence during the early years of the war a study of the problem was initiated by the Air Surgeon. The hemolytic streptococcus was the chief cause of serious communicable disease and for this reason attention was directed to diseases caused by this organism.

Facilities were established for streptococcal grouping and typing and studies were carried out to ascertain the incidence of streptococcal disease. During the winter and spring of 1944-45 the appearance of a highly communicable sulfadiazine-resistant strain of Group A Type 17 streptococcus presented the opportunity for epidemiological studies of an easily identified specific strain.

The Epidemic.—The epidemic began at Keesler Field, Mississippi¹ and was carried by troop movements to other AAF installations assuming epidemic proportions at Lowry Field, Colorado, and Amarillo Field, Texas. The organism was a Group A Type 17 hemolytic streptococcus which exhibited in vitro resistance to sodium sulfadiazine at serum levels of 125 mg per 100 cc. A notable feature of the epidemic was that an excessive incidence of disease occurred only in units composed of personnel recently inducted into the Army.

Origin of the Epidemic.—On November 20, 1944, a shipment of men arrived at Keesler Field from an induction center in California. Respiratory infections were prevalent during the five day train journey and one man sick prior to entraining complained of fever, malaise, dry hacking cough and pains in the chest. This man was hospitalized with pneumonia four days after arrival at Keesler. Group A Type 17 streptococcus was cultured from his throat swabs on two occasions. During the next four weeks, sixteen men from the squadron to which these California inductees had been assigned developed Group A Type 17 streptococcus upper respiratory disease proved by throat cultures.

The first case of scarlet fever due to Type 17 streptococcus appeared twenty-four days after the introduction of the organism into the population. During the following week three additional cases developed, each caused by Type 17 streptococcus. These cases also occurred in the squadron to which men from California had been assigned. Scarlet fever due to other types of hemolytic streptococci was not observed during this period.

On December 21, 1944, Type 17 streptococcus infection first appeared in another squadron, following which there was widespread and fairly rapid dissemination throughout the post (Table 1).

Sulfadiazine prophylaxis of the squadron originally involved (0.5 gm daily at first and later 1 gm daily), failed to halt the course of the epidemic nor was it effective later when given to all personnel on the post.

In March, 1945 the influx of recruits was halted abruptly. This was followed by a sharp drop in streptococcal disease rates, and they did not again assume epidemic proportions.

In vitro tests of sensitivity to sulfadiazine of this Type 17 streptococcus showed it to be resistant to serum concentrations of sodium sulfadiazine of 125 mg per 100 cc. The organisms tested were not those isolated from the original case, but from cases which occurred two weeks later. It seems unlikely that this characteristic of resistance developed during the initial two week period. Had the original strain been sulfadiazine-sensitive, at least a transient fall in case rates for Type 17 from the sulfadiazine prophylaxis would be expected. No such effect was evident.

Interpost Transfer of the Epidemic Strain.—This "Keesler" strain was transferred to four of seventeen AAF installations receiving troop shipments from Keesler Field.² At each field, Type 17 was not present as a cause of disease at the time of arrival of the Keesler shipments. Men from shipments to these four posts were hospitalized with Type 17 infections within one week after arrival, and subsequently contact infections appeared. At each field the strain remained resistant to sulfadiazine. Amarillo and Lowry Fields were the sites of major epidemics.

At Lowry,⁴ the rates for streptococcal disease were low prior to the introduction of the "Keesler" strain. Sulfaprophylaxis was being used and may have been a factor in this low incidence. During the eight weeks following the introduction of the Type 17 streptococcus, the rates rose to several times their previous levels. This organism was found in the throat cultures of 162 men admitted to the hospital, of which fifty-six (34.6 per cent) had scarlet fever. A striking feature of the epidemic was that 110 admissions (68 per cent) for Type 17 streptococcus infections occurred in men who had arrived directly from Keesler Field (Fig. 114).

The rates for streptococcal disease at Amarillo³ were high at the

time the strain from Keesler was introduced. Coincidental with, but not occasioned by, the arrival of 1300 men from Keesler, the entire personnel at Amarillo were placed on sulfadiazine prophylaxis (1 gm, six days weekly). A transient reduction in hospital admissions for all streptococcal disease occurred, but was followed by a sudden rise. This rapid increase in hospital admissions was impressive because of its occurrence during sulfadiazine prophylaxis, and because of the severity of the illnesses, the incidence of complications and the lack

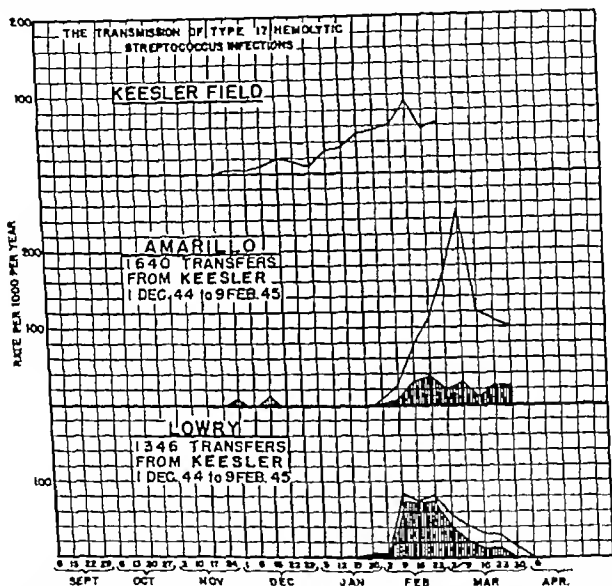


Fig. 114—Showing the transmission of Type 17 hemolytic streptococcus infections from Keesler Field to Amarillo and Lowry Fields (Cross hatched areas represent percentage of total cases occurring in men transferred from Keesler Field)

of therapeutic response to sulfadiazine. In the first two weeks of February thirty two patients entered the hospital with a severe respiratory infection, thirteen of these being recent transfers from Keesler Field. In all cases the organism was Group A, Type 17 streptococcus. Within a two month period, 312 men were hospitalized with respiratory infections caused by this strain of streptococcus. In contrast to the experience at Lowry 19.6 per cent of the cases developed in from Keesler and 80.4 per cent in the Amarillo contacts (Fig 114)

Epidemiology.—The spread of Type 17 streptococcal disease at each post is of interest. An appreciation of the posts in terms of their composition and of the movement of troops through them is necessary to an understanding of the epidemiology. There were three main types of personnel, forming three epidemiological units.

1 The "permanent party" was composed of men who had been in the Army for some years. They were divided into small widely scattered groups, between which there was little contact.

2 The "students or returnees" had had from six months to several years of military experience. They were divided into squadrons for schooling, messing and housing, but the separation was not rigid and there was some intermingling.

3 The "basic trainees" for the most part were men newly inducted into the service. Almost all had less than three months service. They were divided into squadrons by barracks and classes. Members of these units were together throughout the entire twenty-four hours, sometimes under crowded conditions.

From Table 1 it can be seen that the epidemic began in a basic training center squadron (Z-BTC), spread first within that unit, then affected other similar units. From this table it is evident that the basic trainees sustained a higher morbidity from Type 17 infections than troops with longer service. At Amarillo basic trainees also had the highest incidence. Rates for Type 17 infections at Keesler and Amarillo during February and March in basic trainees were about 85 and 860 per 1000 per year respectively. In contrast, in students they were 20 and 105. During the period of the epidemic ninety-five of 2323 basic trainees (4.1 per cent) transferred from Keesler to Lowry and Amarillo became ill with Type 17 disease at some time after arrival, while only three of 413 students transferred (0.75 per cent) were so effected. That this was not due to unequal dissemination is indicated by the fact that streptococcus carrier rates in the two groups were essentially similar upon leaving Keesler.

What Is the Reason for the High Incidence in Basic Trainees?
—Whether the high incidence in basic trainees represents the effect of "seasoning" on susceptibility or reflects environmental and occupational differences cannot be established definitely. The exact nature of "seasoning" is not known. General physical fitness may play a part. For streptococci it may represent a type-specific or possibly a group-specific immunity. It may represent an immunity against the agent or agents of common respiratory disease—diseases which predispose to secondary bacterial invasion.

The evidence is in favor of "seasoning" as the determining factor. Living conditions of trainees and students were similar at Keesler. Known carriers were advanced from basic training to the technical schools, yet the trainees had more disease. A striking feature was the sharp termination of the epidemic when the influx of raw recruits for

TABLE 1—APPEARANCE OF TYPE 17 STREPTOCOCCUS DISEASE AT KEESLER FIELD BY DATE AND SQUADRON

	Number of Cases per Week																											
	18	24	25	1	2	8	9	15	16	22	23	29	30	5	6	12	13	19	20	26	27	3	3	9				
R MD																			1									
II Perm. Party																						1						
O Perm. Party									1						1				1									
B Perm. Party															1				1		1							
A Perm. Party																	1											
P—Perm. Party AM School																						1		2				
K AM. School																				1								
Q AM. School															1													
L AM. School																												
H AM. School																						1						
M AM. School																						2						
I AM. School															1				2		5		8					
D WAC.																			1									
R BTC.										1							3											
X BTC.																						1		3				
U BTC.																1		2		2		5		3				
S BTO																		2		4				1				
T BTC.											1				8		5		2		5		2					
V BTC.											1		1		1		1		3		1							
Z BTC			2		2		4		8		4		2		8		14		11		7		2					

18 24 25 1 2 8 9 15 16 22 23 29 30 5 6 12 13 19 20 26 27 3 3 9
 NOV DEC DEC JAN JAN FEB

MD—Medical Detachment.
 Perm. Party—Permanent Party
 AM. School—Aviation Mechanics School.
 WAC.—Woman's Army Corps.
 BTC.—Basic Training Center.

basic training was halted. At Amarillo the Keesler transfers were assigned to the technical schools and had intimate contact with students who had been stationed at Amarillo for months. The incidence of Type 17 streptococcal disease in the school group among "Keesler"

TABLE 2 —INCIDENCE OF HEMOLYTIC STREPTOCOCCUS CARRIERS IN PERSONNEL TRANSFERRED FROM KEESLER TO AMARILLO

Month	KEESLER						AMARILLO			
	Basic Trainees			Students						
	No Pre-shipment Cultures*	No Group A	Per Cent Group A†	No Pre-shipment Cultures*	No Group A	Per Cent Group A†	No Cultures Taken	No Group A	No Type 17	Per Cent Group A
March	819	59	7.2	600	28	4.7	625	10	7	1.6
April	194	26	13.4	256	25	9.8	278	2	2	0.07

* Cultures taken within forty-eight hours period prior to departure

† Sampling indicated approximately 80 per cent Group A isolates were Type 17

and "non Keesler" men was practically the same 2 per cent and 1.8 per cent. On the other hand, the incidence among basic trainees at Amarillo was eight times greater than in the students. Definite contact with "Keesler" men was not established, although the possibilities for casual and transient contacts were numerous. In spite of quarantine regulations at Lowry, the Type 17 streptococcus was not confined to "Keesler" men as a slight leakage to other personnel occurred.

Factors Influencing Spread of the Epidemic at Each Post.—The spread of this specific strain of streptococcus within each administrative unit was brought about presumably by a combination of direct and indirect means of transmission. The close association of the men in the barracks, classes, and in administrative and communal activities made exchange of organisms by droplet infection probable.

There was ample evidence that environmental conditions were favorable for indirect transmission. Culture plates exposed in barracks yielded Group A Type 17 streptococcus. Cultures taken from blankets, chairs, tables and floors also were positive for the same organism. At Keesler and Amarillo, spread of the epidemic to other units by these fomites was possible.

At Lowry it was possible to institute quarantine measures almost at the beginning of the epidemic. Following the appearance of scarlet fever in men transferred from Keesler all subsequent shipments were quarantined upon arrival. These men were housed and messed separately and particular care was taken to sterilize bedding and eating utensils. Throat cultures were taken on arrival and at three or four day intervals thereafter. All men with evidence of upper respiratory disease or positive throat culture for hemolytic streptococci were hospitalized. Quarantine for each individual barrack was maintained until a period of five days had elapsed without the development of a case of streptococcal infection. In some cases, quarantine lasted three weeks. The failure of the Type 17 strain to spread through the Lowry population is a striking tribute to the effectiveness of these measures.

It is quite clear that sulfadiazine prophylaxis was ineffectual both in preventing the epidemic caused by this strain of streptococcus and in controlling the spread. This demonstrates the importance of learning the degree of sulfadiazine sensitiveness of a given strain of streptococcus before relying on such chemoprophylaxis.

Factors Influencing Interpost Spread of the Epidemic.—Although 17 AAF installations received troop shipments from Keesler cases of Type 17 streptococcal disease occurred only at four and was epidemic at only two. These two fields Lowry and Amarillo received the largest troop shipments. Troops shipped in small groups generally are interspersed with the traveling public. Large groups by contrast travel by individual car or train the dilution factor does not apply and there is ample opportunity to build up an epidemic state within the group. Excessive disease rates for Type 17 streptococcus were found

in four shipments of 715 men to Lowry. For the first week after arrival the incidence rate in these troops exceeded 3000 per 1000 per year, the coincident rate for the field as a whole being less than 300.

The susceptibility of the recipient post to streptococcal disease also must be considered. This may be estimated by a review of the rates for streptococcal diseases during previous epidemic seasons. On this criterion, it is found that Amarillo and Lowry had a high previous incidence of streptococcal disease, while the other installations had a medium or low incidence. In addition, Lowry and Amarillo contained large numbers of technical students, who while more "seasoned" than basic trainees, had, in turn, less service than the more advanced personnel at the group of small posts in which a minimum of Type 17 disease was observed.

During the period of March and April all personnel scheduled to entrain at Keesler Field had swab cultures made from their tonsils and pharynx. All Group A streptococcus carriers were excluded from the shipment (all strains were not typed, but sampling indicated that 80 per cent were Type 17). The low carrier rates in a rather large sample of transferees upon arrival at Amarillo indicates the effectiveness of this procedure. Detection of carriers in this manner in large groups of troops is an ambitious undertaking. When facilities are limited, a maximum return may be expected by limiting such cultures to men from units with significant rates of clinical disease, since such units have demonstrated a high group susceptibility to the strain of streptococcus. Hamburger,⁶ in connection with a study of the "dangerous streptococcus carrier," has shown that individuals most capable of infecting their environment with hemolytic streptococci are those with positive nasal cultures. He showed also that positive nasal cultures are found with greatest frequency in individuals developing streptococcal disease and rarely in the "well" carrier.

Clinical Features.—The clinical features of the "Keesler strain" at the three AAF installations, when local variations in diagnostic criteria were taken into consideration, showed a remarkable similarity between the disease picture at these posts located in climatically different areas. The outstanding difference is the high incidence of streptococcal pneumonia reported from Amarillo. A possible explanation is the clinical impression that many of these cases occurred as a complication of or in association with primary atypical pneumonia.

An analysis of the response to therapy demonstrates the difficulty of recognizing on clinical grounds that an epidemic is due to a sulfadiazine-resistant organism. In patients not seriously ill, equally prompt response to therapy was seen in cases treated with sulfadiazine, penicillin or symptomatically. The more seriously ill patients did not respond to sulfadiazine, but showed prompt improvement following penicillin therapy.

Control Measures.—Perhaps one of the most difficult features is

early recognition of an epidemic or that an epidemic is imminent. The AAF has adopted a system of tabulating upper respiratory disease hospital admissions according to the barrack and unit from which they are derived. Such tabulation provides an overall picture of the incidence and areas of respiratory disease on the post. Knowledge of the previous Army experience of such units is also available and is essential to complete the epidemiologic picture. By means of bacteriologic studies, the variations in specific types of streptococci are followed. A high incidence from one barrack or unit, or a preponderance of one type of streptococcus can thus be detected early and the significance evaluated.

Recently much stress has been laid upon the value of chemoprophylaxis. Sulfonamide prophylaxis has been shown to be effective in the prevention of the transmission of streptococcal disease by reducing both the disease and carrier rates.^{6, 7, 8} The epidemic reported here emphasizes that chemoprophylaxis is no panacea in prevention. Chemoprophylaxis is of value only when the organism is drug sensitive.

Good sanitation, effective quarantine of contacts, segregation of patients, and the detection of carriers remain of paramount importance.

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THE DIAGNOSIS AND TREATMENT OF REITER'S SYNDROME

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IN Reiter's original description of a syndrome characterized by nonspecific urethritis, conjunctivitis and arthritis, he had found a spirochete in the blood of his patient, and therefore termed the disease "spirochaetosis arthritica"¹ This conclusion has since been discredited, but the condition is still called "Reiter's syndrome" Additional cases of Reiter's syndrome have been reported by European authors, and Bauer and Engleman, in 1942, reported the first cases recognized in this country² Excellent reviews of the literature are available^{4 6}

In the Rheumatic Disease Center at Ashburn General Hospital, fifty-three cases of a type similar to this syndrome have been seen The first twenty-five of these have been previously reported³ The purpose of this report is to describe the variations of this peculiar symptom complex, suggest a new term, and present observations based on what is apparently the largest series of cases so far studied

CASE REPORTS

CASE I—In May, 1945, without sexual exposure or previous history of genito-urinary or joint infection, this 25 year old soldier developed a fairly abundant urethral discharge Repeated smears and cultures of the discharge were negative for gonococci He was given sulfadiazine empirically, but the discharge persisted for three weeks One week after the development of the discharge he developed an acute, purulent conjunctivitis in the left eye That same day he developed redness, tenderness and swelling in the dorsum of the left foot He ran a daily temperature up to 101° F for about ten days, after which fever, conjunctivitis and urethritis disappeared At this time, however, the right knee became red, swollen and tender, and effusion developed Cultures of the fluid from the knee were sterile, as were earlier cultures of the conjunctiva The sedimentation rate of the erythrocytes was 38 mm per hour The leukocyte count was 11,200, with 72 per cent neutrophils Typhoid vaccine fever therapy was used, but had little effect The joint inflammation slowly subsided, and after four months the only residual of the disease was slight quadriceps atrophy in the right thigh X-rays showed mild osteoporosis of the bone ends about the right knee No recurrence of urethritis or conjunctivitis was noted and the patient's general condition was excellent

CASE II—This 29 year old soldier had had gonorrhea in 1939 which responded promptly to sulfanilamide In 1942, while at a camp in Texas, the patient developed a nonspecific urethral discharge without sexual exposure About one third of the men in his barracks developed a similar condition, and despite frequent and careful examination by smear and culture, none were found to have gonorrhea

From Ashburn General Hospital, McKinney, Texas

The urethritis disappeared spontaneously in about three weeks. The patient was perfectly well until September 1944 when again without sexual exposure, he developed urethral discharge in which no gonococci could be found in smear or on culture. Accompanying this was a transient mild diarrhea. Two weeks later he developed redness, swelling and tenderness in the right foot, right ankle and left elbow. No conjunctivitis was noted. He received generous doses of sulfadiazine and was given 500 000 units of penicillin without effect on the discharge or the joints. He had a mild fever for two weeks accompanied by a slight leukocytosis and an increase in the erythrocyte sedimentation rate to 28 mm per hour. The discharge gradually diminished and disappeared within six weeks. At that time he developed circinate lesions of a superficial type on the glans penis. Darkfield examination of these lesions showed no spirochetes and culture showed only a scant growth of nonhemolytic *Staphylococcus albus*. The lesions disappeared in three weeks only to recur again for two additional weeks. Urethral discharge was again noted three months after the onset of his disease and again showed no gonococci on smear culture. The joint swelling gradually diminished and finally disappeared completely four and one-half months after the onset of his disease. A follow-up letter from this patient nearly a year later discloses that he has had no recurrence of urethral discharge or arthritis.

CASE III.—This 30 year old soldier developed superficial ulcerations on the glans penis in June 1942. Repeated darkfield examinations showed no spirochetes. Three weeks later and without sexual exposure he developed a purulent urethral discharge. Smears and cultures for gonococci were negative on six occasions. Two days after the onset of discharge he noted redness, tenderness and swelling of the right knee, left foot and the right ankle. The discharge did not respond to adequate dosage of sulfathiazole and the penile lesions did not heal with the application of sulfathiazole powder. He was treated with salicylates for ten weeks and the discharge and joint swelling disappeared. The penile lesions recurred from time to time without other symptoms. No conjunctivitis was noted in this first attack.

The patient was well except for occasional pain in the left foot on walking until November 1944. At this time he again developed a mild purulent urethral discharge followed in one week by bilateral conjunctivitis, low grade fever and swelling, redness and tenderness in the toes of both feet, both knees and the left elbow. A mild leukocytosis was noted and the sedimentation rate was 28 mm per hour. Penicillin (800 000 units) was given, but had no effect on the urethral discharge, conjunctivitis or joint involvement. The conjunctivitis subsided spontaneously in ten days but a scanty urethral discharge persisted. Repeated attempts failed to demonstrate any gonococci.

Two months after the onset of this second attack the patient developed large flat pustules on the soles of the feet and on the lower legs. Thick keratotic crusts gradually developed upon these initial lesions which did not scale off until they were 4 or 5 mm thick. Ulcerations on the glans penis were again noted this time more numerous. The pustular lesions involved the toenails and several of these sloughed out, healing with a dry keratotic bed. At this stage of the disease the conjunctivitis recurred, and acute iritis developed after about one week. A low grade septic fever was present for about four weeks. Typhoid vaccine fever therapy was attempted and a mild improvement noted. The iritis subsided, and within seven weeks all the keratoderma had disappeared. The swollen tender joints continued to be troublesome in spite of physical therapy but by the end of the fifth month of his disease the only residuals were a slight stiffness in the right knee and the toes of the left foot. In a follow up letter six months after discharge the patient stated that he had had no recurrence of discharge or arthritis still had occasional recurrence of penile lesions but no other difficulty.

CASE IV—This 23 year old soldier developed a nonspecific urethritis in May, 1943. This was followed in three days by bilateral conjunctivitis, and acute arthritis of both ankles and knees. Treatment with sulfadiazine had no effect on his illness. The urethritis cleared in three weeks, the conjunctivitis in two weeks, and the joints returned to normal in two and one-half months. Again in June, 1944, the entire episode was repeated and this time four months elapsed before remission occurred. Following his second attack some soreness and stiffness in the ankles and knees persisted.

In May, 1945, following sexual exposure, the patient was found to have a purulent urethral discharge from which no gonococci could be isolated. Within a week he developed acute conjunctivitis in the left eye, and swelling and tenderness in the right knee and both ankles. Cultures from the eye and from the synovial fluid obtained from the right knee showed no growth. Sedimentation rate was 36 mm per hour and the leukocyte count was 11,000 per cubic millimeter. He received no specific therapy. The urethritis, conjunctivitis and arthritis all completely cleared up within three months and the patient was discharged without residual joint deformity.

CASE V—This 26 year old soldier developed purulent urethral discharge without history of sexual exposure in April, 1945. Smears and cultures were negative for gonococci. A few days later swelling, tenderness and redness developed in the right knee and left ankle, and pain developed in both hips. A few days later he was admitted to a hospital overseas where a moderate fever was recorded and flat pustules were noted on the legs and feet. The sedimentation rate was elevated and the leukocyte count was 12,700 per cubic millimeter. The lesions gradually became keratotic and were accompanied by superficial localized ulcerations on the glans penis. Although no specific organism could be isolated from the urethral discharge, skin lesions or joint fluid, he was given 1,000,000 units of penicillin without appreciable effect. He was transferred to Ashburn General Hospital for further care. On examination dry, thickly crusted lesions were present on the soles of the feet and the pretibial areas of both legs. Penile ulcerations were also present, but the urethral discharge had disappeared. X-rays of the knees and left ankle showed moderate bony atrophy. Two weeks after admission here the urethral discharge recurred and swelling and tenderness were increased in the right knee and left ankle. This discharge was again bacteriologically negative and cleared up spontaneously in three weeks. The keratoderma disappeared after two months. The joint involvement disappeared three and one-half months after onset. No residuals were noted. A follow-up letter two months after discharge from the hospital revealed no recurrence to date.

COMMENT

These five cases illustrate some of the variations in the clinical picture of this condition. Though they appear similar, all of these could not correctly be termed Reiter's syndrome as in two cases conjunctivitis was absent. That this conjunctivitis is variable in its occurrence with the disease is demonstrated in Case III, in which it was absent in the first attack but present in severe degree in the second. The so-called "classical triad" has been present in thirty-two of our fifty-three cases. Balanitis circinata was found in twenty-six cases, as often in the cases without conjunctivitis as in those with eye lesions. Six of our patients had keratoderma blennorrhagica without gonorrhea as a part of the disease.

Observations on these fifty three cases, which appear so similar clinically have convinced us that this infectious process has apparently only two constant findings namely urethritis which is nongonorrheal and arthritis. The term "infectious ur arthritis" is suggested to cover this whole group.

To show the probable interrelation and sequence of the types of ur arthritis, Figure 115 has been devised. From this chart gonorrheal arthritis would be gonorrheal ur arthritis. Reiter's syndrome would be nonspecific ur arthritis with conjunctivitis and so forth. Chronic nonspecific ur arthritis could cover both chronic rheumatoid arthritis in which there is a genitourinary focus of infection, and the so-called

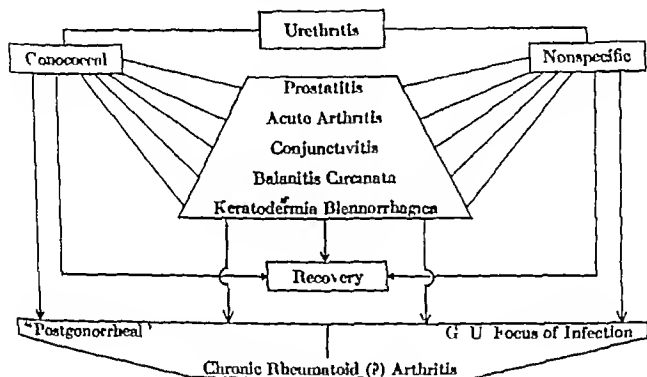


Fig 115—Genitourinary infection with arthritis (infectious ur arthritis)

"postgonorrheal rheumatoid arthritis" which is often also accompanied by a chronic prostatitis in which gonococci no longer can be found. The chart shows that, regardless of etiology a similar sequence of events might occur. If the causative organism of the nonspecific type is found, it will readily fit into place under this terminology.

ETIOLOGY

The etiology of this disease process is so far unknown. That it is of infectious origin seems probable from the onset and course of each case. Many infectious agents have been advanced as the causative organism including the *Spirochaeta* forms, a staphylococcus, an enterococcus, a filtrable virus, and pleuropneumonia like (L) organisms. None of these have been confirmed. Even the portal of entry of the

infectious agent is not definitely established. In most cases a urethritis is the initial symptom, but in some instances the process starts with diarrhea, in others with conjunctivitis, and in a few the arthritis is the first symptom. In all, however, the other symptoms appear in fairly quick succession.

DIAGNOSIS

The establishment of the diagnosis of Reiter's syndrome depends so much on the clinical pattern of the disease that a summary is given below.

- 1 Acute nonspecific urethritis develops often without history of sexual exposure. This may be accompanied by mild, transient diarrhea.

- 2 Within ten days a mild but purulent conjunctivitis develops which disappears in five to ten days, regardless of treatment.

- 3 Within two weeks after onset of discharge, an acute polyarthritis is noted, without chill, but with temperature elevation to about 101° F daily for about ten days.

- 4 Weight loss and muscle atrophy are often marked and develop fairly rapidly.

- 5 The urethritis clears spontaneously after three to four weeks regardless of treatment, but may recur sporadically.

- 6 About one month after onset, superficial ulcerations are noted on the glans penis (balanitis circinata) in many cases, and at this same time keratodermic lesions may be found on the feet and legs in some.

- 7 The sedimentation rate is most rapid about six weeks after onset, gradually returning to normal within three months.

- 8 The keratoderma usually clears in two months. Balanitis may be recurrent independent of the existence of urethral discharge.

- 9 Roentgenograms of the involved joints usually show osteoporosis of the approximating bone ends during the second or third month of the disease. Periosteal proliferation near involved small joints is noted in some cases.

- 10 Within four to six months, under supportive treatment, the involved joints appear normal, the muscles have regained their strength, all skin lesions have healed, the sedimentation rate and blood count are normal, and the changes previously seen on x-ray either have disappeared or are less marked.

The differential diagnosis from gonorrheal arthritis is most important, as the condition is very similar clinically. Careful and repeated bacteriological studies are needed. The gonococcus complement fixation test, when employed, has been reported negative in cases of Reiter's syndrome unless there has been a previous gonorrheal infection. The chill, which so often accompanies the onset of gonorrheal arthritis, has been conspicuously absent in all our cases. The failure of Reiter's syndrome to respond to chemotherapy is a most striking

DIFFERENTIAL DIAGNOSIS OF INFECTIOUS UR-ARTHRITIS

	Reiter's Syndrome	Gonorrheal Arthritis	Rheumatic Fever	Rheumatoid Arthritis
Age and Sex	Nearly always young males—ages 19-38.	Males in ratio 3 to 1 ages 16-40.	Usually ages 6-30. Either sex.	Usually ages 20-40. Females in ratio 3 to 1
Family History	Nearly always absent.	Nearly always absent.	Very often present.	Often present.
Characteristic Onset	Urethritis, usually without sexual exposure. Conjunctivitis and skin lesions with arthritis.	Sexual exposure, then urethritis, prostaticitis and polyarthritis.	Respiratory infection, then fever with migratory arthritis.	Usually insidious, with prodromes of arthralgias, anemia, weight loss. Gradually spreads.
Genitourinary Infection	Urethritis, prostaticitis, perhaps cystitis.	Specific urethritis and prostaticitis.	None or coincidental infection.	Rarely chronic prostatitis.
Characteristic type of Arthritis	Acute onset, marked inflammation, polyarticular, never suppurative, tends to be asymmetrical.	Very acute onset, polyarticular tends to become monoarticular. Often suppurative.	Acute onset, migratory polyarticular transient involvement.	Progressive involvement, usually symmetrical, polyarticular insidious spread to new joints.
Characteristic Eye Lesions	Conjunctivitis (80%) Rarely iritis, keratitis.	Conjunctivitis (15%) Iridocyclitis, ophthalmia.	Very rare.	Iritis, conjunctivitis—very rarely.
Characteristic Skin Lesions	Balanitis circinata in 80%, keratoderma in 10%, mouth lesions rarely.	Purpuric rash, rarely keratoderma. Bleeding hemorrhages in about 5%.	Erythema multiforme or marginatum seen occasionally—nodules.	Nodules found occasionally, psoriasis occasionally.
Cardiac Involvement	Electrocardiographic changes found rarely.	Endocarditis rarely.	ECG changes very often, endocarditis, etc.	Lesions rarely found clinically.
Febile Course	Low-grade, recurrent for 3-3 weeks.	Usually mild, high fever with arthritis.	Usually fairly high and sustained.	Occasional, low-grade, remittent.
Bacteriological Findings	No organisms found, except a few contaminants.	Gonococci from urethra, often from joints.	Hem. strept. often in pharynx.	Indefinite.
Characteristic Course	Severe in early stage, self-limited, lasts 3-6 months.	Usually severe and destructive, may be self limited.	Joint involvement mild. Heart lesions often severe.	Progressive and destructive, exacerbations and partial remissions.
Response to Therapy (Chemotherapy Fever)	Not affected by sulfonamides or penicillin.	Responds to sulfonamides or penicillin or fever.	Salicylates control fever helpful to joints.	No response to sulfonamides or penicillin.
Sequelae and Recurrences	Residuals mild or absent. Recurrences in about 15%.	Destruction of joints common. Rarely recurs.	Heart lesions persist. Recurrence frequent.	Multiple deformities. Chronic and progressive.

differentiation point. Permanent joint damage has been almost completely absent in our series. The accompanying table summarizes differential diagnosis from gonorrheal arthritis, rheumatic fever and rheumatoid arthritis.

TREATMENT

Although the prognosis for this condition is good, several important points should be emphasized in caring for these patients.

1. Penicillin and sulfonamide therapy may be tried, but *only* after repeated and careful studies have absolutely ruled out gonorrheal infection. Many cases are confused by inadequate study and eager institution of chemotherapy. If the disease responds to chemotherapy

the diagnosis of Reiter's syndrome (or nonspecific infectious ur-arthritis) becomes doubtful

2 Salicylates, in doses of 8 to 10 gm daily, are helpful in controlling joint pain

3 Bed rest should not be prolonged, as muscular wasting often becomes quite severe. Physical therapy and exercises for the involved joints must be begun early to prevent deformities which slow convalescence. Hot baths, baking and massage, and properly controlled exercises for the involved parts appear to hasten recovery greatly, and prevent residual disability

4 Symptomatic therapy for the eye and skin lesions are perhaps helpful, as are bland urethral irrigations and hot sitz baths for the genitourinary infections, but vigorous therapy may be harmful, prolonging the natural self-limited course of these infections

5 When the diagnosis has been established, the patients should be reassured concerning prognosis

6 A course of fever therapy by intravenous injection of typhoid vaccine may be attempted in the most severe or persistent cases. This has seemed to hasten recovery in some of our cases

7 Chrysotherapy has little place in the treatment of Reiter's syndrome, as the usual course of gold therapy is too prolonged and the drug too potentially toxic to justify its use in this self-limited condition

CONCLUSIONS

1 From observations in fifty-three cases certain clinical features of infectious ur-arthritis, etiology unknown, have been described. The term Reiter's syndrome should be reserved for those cases presenting the classical features of the disease, namely nonspecific urethritis, conjunctivitis and arthritis. Thirty-two of our fifty-three cases exhibited this triad. Skin lesions, particularly penile ulcerations, are commonly found

2 The condition must be carefully differentiated from gonorrheal arthritis, rheumatic fever and rheumatoid arthritis

3 The disease is self-limited with few residuals, but recurrences have been noted in 15 per cent of the cases. Prognosis for recurrences is as good as in the original attack

4 Because of the good prognosis, treatment should be directed to hastening the convalescence

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SPLENOMEGALY

THE DIFFERENTIAL DIAGNOSIS OF SPLENOMEGALY OF ADULTS

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SPLENOMEGALY is often an unexpected physical finding and it immediately presents numerous diagnostic possibilities. Since the condition may be of sufficiently uncommon occurrence in general practice to allow memory of the diagnostic possibilities to become hazy and yet common enough to be a constant threat, it is felt that a review of the differential diagnosis of the more common types of splenomegaly of the adult will be acceptable. A presentation of some representative cases may be helpful in illustrating diagnostic points.

No attempt is made in this presentation to cover systematically all types of splenomegaly nor to give a textbook description of the specific diseases involved. Rather the attempt has been to select a group of interesting and illustrative cases for this clinic. Many conditions have not been illustrated for example space is not given to chronic malaria, syphilis, tuberculosis, kala azar and other conditions in which the splenomegaly probably would become apparent in the systematic diagnostic work up of the patient. Here, history of residence and exposure, routine specific tests or more apparent diagnostic features of the disease will help to account for the associated splenomegaly. Some of the cases presented may not be of very common occurrence but I trust that their interest will justify their inclusion in the group.

It should be appreciated that most diseases of the spleen are dependent on disturbances of the structure, circulation, or other physiologic functions of that organ. For this reason a general

knowledge of the anatomy and physiology of the spleen,¹¹ so far as it is known, is helpful. From this knowledge it is possible to postulate pathologic changes to explain laboratory and physical findings and to narrow down the diagnostic possibilities.

ANATOMY AND PHYSIOLOGY OF THE SPLEEN

The spleen is situated in the left hypochondriac region, between the fundus of the stomach and the diaphragm. The border which extends a variable distance into the peritoneal cavity is not ordinarily palpable. In questionable cases the spleen can be felt, when the patient inspires deeply, with a supporting hand or arm under the left flank to force the viscera as far forward as possible. Occasionally, it is more satisfactory to turn the patient on his right side, urging complete relaxation, and allowing the weight of the spleen to drag it down to the costal margin, another alternative is to cause the spleen to be forced down by coughing. Occasionally, again, the spleen can be felt with the patient standing. It should be emphasized that, due to the mobility of some spleens, they can be palpated at the time of one examination but not at another, unless some of the above manipulations are employed to bring the organ into the field of examination.

An understanding of the vascular supply (fig 116) of the spleen will explain some of its pathologic changes. The splenic artery arises from the celiac axis, courses laterally along the upper border of the pancreas, supplying that organ, and then gives off the left gastroepiploic and short gastric arteries. Shortly before the splenic artery reaches the hilus of the spleen it divides into a number of branches which enter the organ as end-arteries. This point is important since end-arteries permit infarction, a common complication of most types of splenomegaly, often giving rise to obscure, and occasionally to severe, abdominal crises. These hilar arteries traverse the fibrous trabeculae of the spleen for a short distance, dividing into smaller vessels as they ramify through the organ. When the vessels have repeatedly branched until they are about 0.2 mm in diameter, they leave the fibrous trabeculae and enter the substance of the spleen, becoming surrounded by a mantle of lymphatic tissue, the malpighian corpuscle. Such an artery is now known as the "central artery." During its course through this lymphatic follicle, the central artery gives off thick-walled capillaries and eventually these capillaries open into the pulp spaces. The artery itself continues through, and out of, the corpuscle to the endothelial capillaries of the ellipsoids. There is controversy yet as to whether this is an open or closed circulation but the consensus seems to be that, under

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with changing splenic function, blood cells can either enter or leave the pulp spaces by the capillaries which connect the arterioles and venules

The tough, fibrous capsule of the spleen is covered by the visceral peritoneum. The trabeculae of the spleen are then built in from this capsule as ramifications of fibrous, partial partitions which eventually divide the organ into a maze of intercommunicating spaces. These spaces contain the pulp substance. Some smooth muscle cells are found in these trabeculae and in the capsule, their activity causing contraction of the organ, while the large amounts of elastic tissue present make possible great variation in its size. The pulp spaces are lined by the reticulum cells, which are primitive cells derived from the mesoderm. Structurally they have a fine chromatin network, with a sharp nuclear membrane and a variable amount of cytoplasm. These cells nest together, making up a syncytium and they have great phagocytic potentiality. This function undoubtedly is of great importance in many of the more common destructive diseases such as the hemolytic anemias, thrombocytopenic purpura and splenic neutropenia. These primitive cells of the reticulum can become free histiocytes. They probably retain primitive potentialities of the mesoderm and, with adequate stimulus, give rise to the various types of blood cells.

As was stated before, the spleen can vary greatly in size and normally a quiet, periodic, rhythmic contraction of this organ pumps the blood into the splenic vein. During periods of relaxation the splenic sinuses are large and filled with blood elements. Normally there is considerable stagnation of flow, with pools of accumulated blood cells in the pulp sinuses. This arrangement puts the blood cells in immediate contact with the reticulum cells, an ideal situation for phagocytic destruction under physiologic or pathologic conditions. This arrangement also allows accumulation of large numbers of noncirculating cells and these accumulations constitute reservoirs of cells that can be thrown into the general circulation by powerful contraction of the spleen. Such contraction is caused by stimulation of the cervical sympathetic division of the autonomic nervous system. Injection of epinephrine, therefore, will cause such contraction and this procedure is helpful at the time of splenectomy, in certain diseases, when the patient can be given a so-called auto-transfusion of this large reservoir of blood cells before the splenic pedicle is ligated.

The splenic vein is of great interest in any consideration of the spleen. This vessel is formed by confluence of the trabecular veins of the spleen at the hilus. It passes medially along the upper border of the pancreas, receiving the left gastro-epiploic vein, short gas-

tric and pancreatic tributaries, the inferior mesenteric vein and finally joins the superior mesenteric to form the portal vein. The splenic vein is larger in caliber than its companion artery, a structural difference undoubtedly secondary to the periodic increase in volume of blood which occurs with splenic contraction. There is evidence to suggest that the splenic vein can contract (remarkably so in the dog) with reduction of venous flow and increased congestion in pulp sinuses. Another important anatomic fact is the lack of valves in the splenic vein and portal system, a condition which allows reversal of flow in case of portal obstruction and accounts for collateral circulation, giving rise to varices of the esophagus among other effects.

ABNORMAL HEMOPOIESIS

Pernicious Anemia—Pernicious anemia in severe relapse often will be accompanied by splenomegaly, although this may not be an outstanding feature. The splenomegaly may confuse the diagnosis however because of the signs of hemolysis that are present and may give the impression that the condition at hand is primary hemolytic anemia. Pernicious anemia is fundamentally a deficiency disease in which the intrinsic factor is no longer produced by the atrophic gastric mucosa. In the normal individual, this intrinsic factor unites with the extrinsic factor or with protein substances present in the diet to form the factor which causes maturing of the erythrocytes and which is necessary for the bone marrow to develop a normoblastic line of erythrocytes. Without this substance, there is a shift to a megaloblastic type of marrow in which abnormal red blood cells are formed. Probably because of this abnormality the cells are destroyed in large numbers by the spleen and a hemolytic process becomes prominent, giving the lemon yellow tinge to the scleras and skins of such patients. There is an associated achlorhydria and proof of its presence should be elicited by stimulation with histamine at the time of analysis of gastric content. Examination of the blood smear gives evidence of a macrocytic type of anemia, in which poikilocytosis is usually an outstanding feature. Red blood cells may number less than 1 000 000 per cubic millimeter of blood and there is almost always an associated leukopenia. Practically always some hypersegmented ("right shifted") neutrophils are present, while myeloid immaturity often severe enough to suggest leukemia is a common finding in the presence of severe relapse. Finding of megaloblasts in the blood smear is not an uncommon occurrence in this type of case and sternal aspiration performed on the untreated patient reveals a megaloblastic marrow. It is rare, however in these days of promiscuous treat-

Kline test for syphilis negative

Serum bilirubin direct negative

indirect, 1.8 mg per 100 c.c.

Stools for occult blood negative

Roentgenologic examination of thorax and stomach negative

Excretory urogram essentially negative except that the left kidney was compressed and displaced medially by a large extrarenal mass, probably spleen

Intensive treatment with liver extract was started and in the ensuing three weeks the concentration of hemoglobin rose from 8.5 gm to 13.8 gm per 100 c.c. Red blood cells numbered 3 460 000 and leukocytes 5 000 per cubic millimeter of blood at the time of the patient's dismissal. The value for reticulocytes was 5.9 per cent six days after the first injections of liver had been given by us. During this period the spleen became considerably smaller. The patient remained well on a maintenance program of treatment by liver extract.

Discussion of Case 1—The pernicious anemia in this case might well be confused with one of the varieties of hemolytic anemia in view of the moderate splenomegaly, icterus, anemia, crisis like onset of symptoms and elevated value for the indirect serum bilirubin. The morphologic changes of the blood cells are very helpful here since there were macrocytosis and poikilocytosis of the red blood cells with associated hypersegmentation ("right shift") of the neutrophils. The increased regeneration is explained by the history of previous injections of liver extract. In most of the hemolytic states the red blood cells are characterized by spherical microcytosis while the amount of regeneration usually is definitely high. The normal fragility of the red blood cells does not exclude a hemolytic state but makes it less likely. It should be remembered that patients who become affected with insidious anemia may tolerate very low values for hemoglobin before they note symptoms, therefore, sudden collapse may be the supposed onset of the disease. Had the anemia in this case been due to a bleeding lesion there would have been a hypochromic picture, with increase in regeneration of red blood cells since in these circumstances there is constant loss of body iron. This type of loss does not take place with uncomplicated pernicious anemia or a hemolytic state. The high incidence of gastric lesions among people who have pernicious anemia must be remembered and it is not unusual to find a bleeding lesion with the associated hypochromic anemia in examination of a patient who is suffering fundamentally from pernicious anemia.

Leukemias—Leukemia is probably the commonest cause of persistent and great splenomegaly. While in some of the acute leukopenic or aleukemic forms of leukemia a severe systemic reaction may be present without splenomegaly, the reverse usually is true. Generally splenomegaly is the subject of one of the early complaints of the patient or is one of the early findings of the physician. Leu

kemia, as yet, is of unknown etiology and it terminates in death of the patient in a variable period of time. The acute forms of the disease usually terminate within a few months, while the chronic form may exist for many years. The disease is characterized by uncontrolled proliferation of the leukocytes and of their precursors, in the hemopoietic tissues and later in all of the tissues of the body. The symptomatology may be extremely variable and in part may depend on the organs most prominently involved. Anemia is usually an early symptom, due to reduced erythropoiesis, while fever, loss of weight, weakness and malaise are of common occurrence. The diagnosis depends on demonstration of the leukemic cells in the peripheral blood or in the blood-forming organs. If the leukocyte count is high and immaturity of leukocytes is prominent, the diagnosis is not difficult. In leukopenic forms of leukemia there may be much doubt and even the trained microscopist may have difficulty in establishing the diagnosis. In the leukopenic forms, ability to recognize both immature features and bizarre or abnormal morphologic changes in the circulating cells is essential for diagnosis.

CASE 2 *Chronic Myelogenous Leukemia*—A white woman, twenty years of age, was admitted to the Clinic with a diagnosis of leukemia. Eleven months before admission, she had noted a mass in the left side of the abdomen but had no other symptoms. Her physician had diagnosed this as an enlarged spleen and she had been sent to a hospital where studies of the blood resulted in a diagnosis of leukemia. She had been given roentgenologic treatment, which caused the mass to disappear. Ten months later, however, a similar mass had been noted and she came to the Clinic for advice. Her only other complaints were of weakness and ease of fatigue.

The woman was well developed and well nourished. Physical examination disclosed nothing remarkable except moderate anemia and a spleen tender to pressure, which filled the left upper quadrant of the abdomen. Laboratory work revealed the following:

Urinalysis negative

Hemoglobin 7.7 gm per 100 c.c. of blood

Erythrocytes 2,420,000 per cu mm of blood

Leukocytes 210,000 per cu mm of blood

Differential leukocyte count, per cent

lymphocytes,	2.5
monocytes,	0.5
neutrophils,	56.0
eosinophils,	2.0
basophils,	7.0
metamyelocytes,	8.0
myelocytes,	2.0
promyelocytes,	8.0
leukoblasts,	3.5
stem cells,	0.5

Blood smears "chronic myelogenous leukemia"

Kline test for syphilis negative

Thoracic roentgenogram negative

Discussion of Case 2—This case is rather typical of myelogenous leukemia, the patient presenting herself with a large, tender spleen, vague malaise and weakness. Physical examination revealed the splenomegaly. The blood findings were characteristically diagnostic, showing a very high total blood count, with myeloid immaturity of all forms back to the stem cell and associated anemia. The blood picture is the most helpful diagnostic aid in this type of case, while the temporary favorable response to roentgen therapy further supports the diagnosis. An occasional patient may be encountered whose disease is in remission induced by roentgen therapy and then it may be impossible to make the diagnosis. Usually, it is best to continue observation until the characteristic signs and symptoms return.

CASE 3 Chronic Myelogenous Leukemia—A white male professor fifty three years of age, came to the Clinic complaining of pains in his legs. He gave a clear history of intermittent claudication and a diagnosis of arteriosclerosis obliterans was made. However a spleen extending almost to the pelvic brim and to the right of the midline was found. Physical examination otherwise did not disclose anything remarkable. There was some vague history of abdominal distress but no other complaint relative to the abdomen was obtained. Laboratory findings were as follows:

Urinalysis essentially negative

Hemoglobin: 10.6 gm. per 100 c.c. of blood

Erythrocytes 3,260,000 per cu. mm. of blood

Leukocytes 10,500 per cu. mm. of blood

Platelets 174,000 per cu. mm. of blood

Blood smear myeloid immaturity of all forms back to the stem cell with marked changes in the red blood cells (poikilocytosis, polychromasia, basophilic stippling and occasional normoblast)

Sternal aspiration considerable increase in the buffy coat layer indicating marked hyperplasia. Examination of the smears disclosed marked left shift, with large increase in stem cells.

Blood urea 40 mg. per 100 c.c.

Calcium 9.1 mg. per 100 c.c. of serum

Cholesterol 127 mg. per 100 c.c. of plasma

Cholesterol esters: 75 mg. per 100 c.c. of plasma

Lecithin 170 mg. per 100 c.c. of plasma

Total fatty acids 247 mg. per 100 c.c. of plasma

Total lipoids 374 mg. per 100 c.c. of plasma

The roentgenogram of the thorax gave evidence of a healed primary complex, with scattered miliary calcification in both pulmonary fields.

A diagnosis of chronic leukopenic myelogenous leukemia was made. Roentgenologic treatment was followed by considerable improvement in the patient's general physical condition. Thereafter the patient returned periodically for treatment and he remained in relatively good health except for recurring attacks of gout. In 1943 the value for uric acid was found to be 6.7 mg. per 100 c.c. of blood (normal 2 to 4.5 mg.). Since then, he has been on a regimen for gout, including the taking of acetylsalicylic acid as a urate diuretic and a strict purine-free diet. As in many of these blood dyscrasias, however the

concentration of uric acid rises rapidly when acetylsalicylic acid is not taken and repeated mild attacks of gout have been frequent

Discussion of Case 3—This case illustrates rather typical leukopenic myelogenous leukemia, with its very insidious onset and with discovery of the disease being almost accidental because of examination for another complaint. Here the large spleen was found on physical examination, while the myeloid immaturity found in the blood smear suggested the diagnosis. The discovery, on sternal aspiration, of markedly hyperplastic marrow and a large number of stem cells established the diagnosis. Another interesting feature of the case is the presence of gout and it should be remembered that, in many cases, gout may be a presenting complaint of the patient before there is any other evidence of a leukemic process. Consequently, patients who have gout should be investigated with the possibility in mind of an associated blood dyscrasia, particularly leukemia or polycythemia.

CASE 4 Chronic Lymphatic Leukemia—The patient was a white man, forty-nine years of age, who came to the Clinic in 1940 complaining of heart consciousness and a slow pulse. There was no evidence of organic heart disease at that time and physical examination otherwise did not reveal anything remarkable. The man was 6 feet (182.9 cm) tall and weighed 254 pounds (115.2 kg).

The patient returned the following year because he had noted, during the previous six months, the appearance of enlarged glands in his neck. He also had become nervous and irritable, mild tremor had developed and he had become increasingly tolerant to cold, so that a warm house gave him considerable distress. He complained of weakness of the muscles of his legs and had noted palpitation of the heart and increased dyspnea with exertion.

The thyroid gland was enlarged to two or three times its normal size and blood pressures were 148 mm of mercury systolic and 110 diastolic. There was mild, generalized adenopathy and the tip of the spleen was just palpable. Laboratory work revealed the following:

Urinalysis negative

Hemoglobin 14 gm per 100 c.c. of blood

Erythrocytes 4,820,000 per cu. mm. of blood

Leukocytes 43,000 per cu. mm. of blood

Blood urea 34 mg per 100 c.c.

Basal metabolic rate plus 13 per cent

Differential leukocyte count, per cent lymphocytes 61.0

monocytes, 3.5

neutrophils, 35.5

Blood smear "chronic lymphatic leukemia"

This patient was given roentgen therapy and progressed well for two years. Symptoms of hyperthyroidism persisted, however, and the basal metabolic rate rose to plus 23 per cent. Thyroidectomy was performed in 1943, with marked improvement in the patient's general health resulting and, thereafter, he remained relatively well. He received occasional roentgenologic treatments as they were needed to control his blood picture and adenopathy.

Discussion of Case 4—This case is presented here because of the associated hyperthyroidism, although otherwise it is a typical case of chronic lymphatic leukemia. Since many patients with blood dyscrasias present themselves because of loss of weight, intolerance to heat, increased tolerance to cold, excessive sweating, weakness and palpitation, the diagnosis of hyperthyroidism may be further supported with an elevated basal metabolic rate. When the patient in this case first presented himself with these complaints and diffuse enlargement of the thyroid gland was noted, together with a basal metabolic rate of plus 13 per cent, his condition was thought to be fundamentally hyperthyroidism. However, considering the leukocyte count of 43,000, the picture of chronic lymphatic leukemia and the adenopathy it was felt that the leukemia was responsible for all of the symptoms. Roentgen therapy was followed by regression of the lymph nodes but by very little alteration in any of the conditions about which the patient originally complained, while his nervousness increased and a tremor became evident. Largely at the patient's insistence, thyroidectomy was performed and the marked alleviation of his symptoms fully justified his demand. The opposite, however, usually is true. In some cases obscure leukemia has been mistaken for hyperthyroidism and full blown leukemia has developed later.

CASE 5 Leukopenic Myelogenous Leukemia—A white man fifty nine years of age, was admitted to the Clinic because of exhaustion and pallor which had been present for about six months. There had been some anorexia and loss of 35 pounds (15.9 kg) of body weight during that period. Nausea had been frequent, with troublesome, occasional vomiting, usually when the stomach was empty. The pallor had become noticeable to the patient's family.

The man was thin, well developed and had a sallow color. His teeth were in poor repair. His heart and lungs were not remarkable in any way. The tip of his spleen was just palpable. Preliminary laboratory work revealed the following:

Urinalysis negative

Hemoglobin: 6.8 gm per 100 c.c. of blood

Erythrocytes 2,000,000 per cu. mm. of blood

Leukocytes 1,200 per cu. mm. of blood

Differential leukocyte count, per cent

lymphocytes 49.0

monocytes 1.0

neutrophils, 45.0

metamyelocytes 1.0

myelocytes 1.0

promyelocytes, 2.0

Blood smears "an increase in regenerative macrocytes, with an occasional late normoblast. Marked leukopenia. No myeloid immaturity found on this smear." Buffy coat or leukocytic cream smears were made but gave no evidence of immaturity other than the presence of a great many normoblasts.

Kline test for syphilis negative

Analysis of gastric contents achlorhydria

Serum bilirubin direct, negative

indirect, 0.8 mg per 100 c c

Sternal aspiration disclosed hyperplastic bone marrow with marked left shift in the myeloid line Many myeloblasts contained Auer's bodies

Roentgenograms of the thorax, stomach, colon and terminal portion of the ileum were negative

A diagnosis of aleukemic myelogenous leukemia, subacute to acute, was made The patient was given two transfusions and was dismissed from our care Word was received of his death three months later

Discussion of Case 5—This case is reported because it presented an obscure diagnostic problem The man's complaints referred, primarily, to the stomach and intestine and included mention of severe exhaustion and anemia Physical examination disclosed nothing remarkable, other than pallor and a palpable splenic tip The rather severe anemia could have been part of any chronic debilitating disease The leukopenia immediately aroused suspicion that a disease of bone marrow was in the background, although occasional transient leukopenia may be picked up routinely when patients are having febrile reactions If patients have chills and fever, marked leukopenia may be present following a chill and in such cases repeated counts always should be made because of fluctuating total counts The myeloid immaturity found in the blood smear is definitely suggestive of a leukemic process but there is not enough to make such a diagnosis with these findings Degenerating hypernephromas or penetrating, silent lesions of the bowel and penetrating carcinomas often can give a marked leukemoid reaction that may be difficult to distinguish from a leukemic picture Examination of repeated blood smears, however, failed to give evidence of any constant immaturity in this case and a leukemoid reaction seemed probable

Gastro-intestinal examination had not revealed anything remarkable and sternal aspiration was performed The diagnosis was definitely established by this procedure, with the finding of a large number of stem cells, but of still greater significance was the presence of Auer's bodies in many of the myeloblasts I have seen Auer's bodies only in relatively acute leukemic processes These bodies, when stained with Wright's stain, are usually spindle shaped rods that take a pink, rather eosinophilic stain and stand out rather prominently in the cytoplasm of the cell Often they overlie the nucleus in a depression which looks as though it had been scooped out of the nucleus Occasionally, this Auer's body material is in the form of fine granules or dust rather than in rods but, due to its rather characteristic color, it still can be identified This patient's subsequent course and death have further verified a diagnosis of an acute, leukopenic myelogenous leukemia

Polycythemia Vera.—Polycythemia vera is a chronic disease of insidious onset. It is characterized by absolute increase in the number of red blood cells and in the total blood volume. There is, undoubtedly, abnormal production of erythrocytes in this disease and the increased blood volume probably is a compensatory phenomenon. Determinations by means of the hematocrit show an increased percentage of blood cells per unit of whole blood. While a normal hematocrit reading averages about 48 per cent red blood cells, the reading in polycythemia vera usually is 60 to 65 per cent but may reach 80 per cent. With this high percentage of red blood cells, there is marked increase in the viscosity of the blood, which undoubtedly accounts for many of the presenting symptoms and, because of the ease with which thrombi form in such blood, the increased viscosity is a common cause of complications. Values for white blood cells, platelets and hemoglobin also are high. The white count commonly is elevated to leukemic proportions and there is often much myeloid immaturity. The skin and mucous membranes of the patient usually are characteristically red. However, the skin may be white. The spleen usually is palpable (75 per cent or more of cases) and may be very large. Due to the bone marrow activity the basal metabolic rate is elevated and some patients have a tolerance to cold that suggests hyperthyroidism. There may be evidence of cerebrovascular accidents, erythromelalgia or other vascular manifestations. Due to the high value for uric acid in the blood, gout and renal colic, the latter attributable to the passage of crystals of uric acid, are not of uncommon occurrence. Duodenal ulcer and other gastro-intestinal complications often are encountered, while cirrhosis of the liver has been reported in many cases. It should be remembered that late in the disease in many of these cases a blood picture typical of myelogenous leukemia develops and the anemia usually associated with that disease appears. In an occasional case the condition is extremely difficult to distinguish from secondary polycythemia but, in such cases, increased blood volume is extremely rare.

CASE 6 Polycythemia Vera.—This patient, a white man sixty three years of age, was referred to the Clinic with a diagnosis of chronic myelogenous leukemia, probable ulcerative colitis and recent attacks of Ménière's syndrome. He registered in May 1943 and gave a history of a troublesome diarrhea with passage of 8 or 10 stools in twenty four hours. He had passed frothy blood at times and the condition seemed to be getting progressively worse. During the period when he was having the foregoing trouble he had noted enlargement of the spleen and the day before his admission results of blood counts had suggested leukemia. The man also had had severe vertigo with vomiting two days before admission. The patient's past history was essentially negative. Two brothers had died, one with cerebral thrombosis and the other with coronary occlusion.

The man was well developed, well nourished and definitely plethoric. He was "warm blooded" and immediately shed his coat after coming into the office. Examination of the heart and lungs gave negative results but the spleen extended downward to the umbilicus. Laboratory findings were as follows:

Urinalysis specific gravity, 1.020

albumin, grade 2

casts, occasional

Hemoglobin 20 gm per 100 c.c. of blood

Erythrocytes 7,550,000 per cu. mm. of blood

Leukocytes 39,200 per cu. mm. of blood

Differential leukocyte count, per cent lymphocytes, 15.0

monocytes, 3.0

neutrophils, 81.5

basophils, 0.5

Reticulocytes, per cent 2.2

Platelets 92,000 per cu. mm. of blood

Blood smear increased piling of the red blood cells with moderate polychromasia and an occasional normoblast, no myeloid immaturity, smears suggest polycythemia vera

Hematocrit 66 per cent red blood cells

Blood volume total plasma, 43 c.c. per kg. of body weight

total whole blood, 131 c.c. per kg. of body weight

Blood urea 50 mg. per 100 c.c.

Uric acid in whole blood 5.8 mg. per 100 c.c. of blood

Proctoscopic examination disclosed punched-out ulcers which were thought to be of the typical amebic type. Stools and scrapings from these ulcers, however, did not yield organisms. Roentgenograms of the colon gave evidence of ulcerative colitis, with minimal changes involving the rectosigmoid. The colon and terminal portion of the ileum were otherwise negative to examination.

The patient was hospitalized because of the condition of his bowel and phlebotomy was performed at various times in the course of the ensuing two weeks to reduce the blood values to normal. The course of the disease was complicated by an acute attack of gout involving both feet and the man had repeated renal colic, with the passage of crystals of uric acid. Following return of the hematocrit values to normal, cerebral manifestations and symptoms referable to the bowel markedly improved. On a regimen for gout the patient was relatively free of trouble. His polycythemia was controlled with the use of radioactive phosphorus.

Discussion of Case 6—This case illustrates polycythemia vera and many of the complications which accompany the disease. There is little that could confuse the diagnosis here.

ABNORMAL DESTRUCTIVE ACTIVITY OF THE SPLEEN

Hemolytic Anemias.—Congenital hemolytic icterus is a satisfying disease to the physician who is responsible for treatment, since splenectomy gives gratifying therapeutic results. Congenital hemolytic icterus must be definitely distinguished from numerous atypical hemolytic states. It is a disease in which the blood cells are characterized by increased fragility (or decreased resistance) when they

are suspended in hypotonic salt solution. Moreover, the blood cells evidently are more susceptible to destructive action by the phagocytic cells in the spleen than are normal cells. This former abnormal characteristic is inherited as a mendelian dominant factor.

In order to make a clear-cut diagnosis, I feel that the following diagnostic features should be present:

1. *A good family history* This may be difficult to obtain from some patients and, in any event, it will be helpful to examine other members of the family for splenomegaly, anemia and the characteristic hemologic finding of the disease. In doubtful cases it is gratifying to be able to demonstrate the presence of the disease in other members of the family.

2. *A personal history of recurring episodes of hemolysis* It is not unusual for people who have this disease to have been partial invalids most of their lives, due to the effect of the chronic anemia. Many, however, who have the disease in a mild form will have little trouble except in periods of crisis. Crises are characteristic of this disease and are episodes wherein acute hemolytic activity ensues. Such episodes may be precipitated by intercurrent infection, trauma, fracture or a surgical procedure. Recovery from such episodes may be rapid or slow, depending on how chronic the condition usually is as it affects the individual patient. Such hemolytic crises, of course, may be fatal due to the profound anemia or the renal damage secondary to the hyperbilirubinemia. The personal history of recurring hemolytic episodes should always be sought.

3. *Splenomegaly on physical examination* This usually is a prominent feature in the congenital or familial case. If the disease has been very mild, the splenomegaly may be equally slight. However, in the average case repeated crises with enlargement and secondary fibrosis in the spleen, usually result in slowly progressive splenomegaly.

4. *Positive laboratory results* All characteristic laboratory findings should be positive and, in any case in which they are not positive, the diagnosis should be accepted with considerable skepticism. These findings are as follows: a. The increased fragility of the red blood cells when suspended in hypotonic saline solutions has been mentioned. b. Spherical microcytosis is evident when the blood is studied on the usual blood smear. This phenomenon is present in most of the hemolytic diseases but always is present in congenital hemolytic icterus. The cells are small, spherical, darkly stained red cells usually of a diameter less than 6.8 microns. If hemolysis is extremely active, and if equally active regenerative bone marrow is present, numerous macrocytic reticulocytes will confuse the uninitiated in examination of such blood smears. These macrocytes, how-

ever, usually will give evidence of polychromasia, chromatin rests or even Howell-Jolly bodies. Numerous immature red cells may be present and there may be a marked leukemoid reaction, with enough myeloid immaturity to confuse the diagnosis with that of myelogenous leukemia. These findings, however, are of a regenerative nature and undoubtedly are due to the effort of the hyperplastic bone marrow to throw all available cells into the circulation. Because of this marked regenerative activity, the reticulocyte count will be elevated and, even in rather mild cases, in which the condition is not in a state of crisis, it is usually more than 5 or 6 per cent. c The anemia in these cases is often the most profound encountered in hematologic diseases. It is not uncommon, in a state of crisis, for the red blood cell count to be less than 1,000,000 per cubic millimeter of blood. The concentration of hemoglobin will be correspondingly low. In an uncomplicated case there is no hypochromasia, since the patient's hemopoietic system is literally swamped with iron from the hemolyzed red cells. d If sternal aspiration is done, markedly hyperplastic bone marrow of the normoblastic type will be found. Many phagocytic cells with ingested debris of red cells may be present. While there will be a left shift in all elements, there is not usually the degree of myeloid immaturity seen with a leukemic marrow. e An elevated value for serum bilirubin, with an indirect van den Bergh reaction is another feature. The degree of jaundice and the amount of bilirubinemia probably are dependent on the ability of the liver to handle large quantities of these pigments. In an occasional case, wherein the liver excretes the bilirubin rapidly, there may be no jaundice and very little increase in the concentration of serum bilirubin, so that examinations of stools may have to be done for excess amounts of urobilinogen. Rarely, the direct van den Bergh reaction may predominate, due to the presence of a stone in the common bile duct or to damage to the liver. Since gallstones develop in 60 or 70 per cent of patients who have this disease, the possibility of there being a stone in the common bile duct must always be considered, although the black, irregular, cinder type of pigment stone that develops in these cases is evidently much less prone to slide through the cystic duct than are the smooth stones characteristic of other biliary disease. If obstructive jaundice is present, stools will be acholic and there will be bile in the urine. In uncomplicated hemolytic disease (acholuric jaundice) the reverse is true.

Most confusing from a differential diagnostic standpoint will be the group of atypical ("acquired") hemolytic anemias of unknown etiology. Any case which does not meet the above criteria of positive family and personal history of the disease, definite spleno-

megaly and positive laboratory findings, should be considered an atypical case (acquired hemolytic icterus) and the prognosis should be qualified if splenectomy is performed. Patients who have an atypical form of the disease, for the most part, present themselves to a physician because of the severe anemia. Splenomegaly is often minimal and it is not unusual for the spleen to enlarge palpably only while the patient is under observation because of acute illness. If however, the process has been more or less active for some time, splenomegaly may be a definite feature of the disease.

There are two hemolytic conditions of atypical ("acquired") type, and of which splenomegaly may be a feature, which should be differentiated because results of treatment in this condition are as satisfactory as are results of splenectomy for the congenital type. The first of these is Lederer's anemia, which is an acute type of hemolytic anemia secondary to an infectious process. While this condition is rare, it should be borne in mind whenever a hemolytic condition is encountered following an infection. It has been found most commonly among children following respiratory infections. Laboratory examination gives evidence of hemolytic anemia and the anemia may be profound. Cases are variable as to other findings. The spleen may or may not be palpable. The red cells may or may not be characterized by increased fragility. Probably spherical microcytosis always is present, together with marked increase in regeneration, and there may or may not be an appreciable change in the concentration of serum bilirubin. There is no previous personal history of hemolysis. True Lederer's anemia is corrected by transfusions of blood, recovery is complete and the condition does not recur.

The other type of hemolytic state that may present splenomegaly is that secondary to repeated transfusion of an Rh negative patient with Rh positive blood. Here the diagnosis rests on the history of repeated transfusions and the appearance of hemolytic reactions following the later transfusions as well as on determination of the presence or absence of the Rh factor in the blood of donors and recipient.

It must be remembered that hemolytic anemia may be a complicating feature of many other diseases in which splenomegaly is a characteristic: leukemia, lymphosarcoma, Hodgkin's disease, syphilis, acute infections which have been combated with chemotherapy, bacterial endocarditis, pernicious anemia in severe relapse and septicemia, to mention only a few. In presence of these conditions, diagnosis of the primary disease is essential. Hemolytic states accompanied by mild icterus and considerable anemia are commonly confused with pernicious anemia.

CASE 7 Congenital Hemolytic Icterus—A white youth, nineteen years of age, was referred to the Clinic in November 1942, suspected of having myelogenous leukemia. He had been seen by his home physician the month before because of fatigue and weakness which had recurred for some years *His mother had stated at that time that he had been treated for anemia many times in the past and that she had never considered him in good health* The mother and father were living and well and the patient was an only child The home physician wrote that he had found the following temperature, 99.6° F., pulse rate, 100 per minute, blood pressures, 140 mm of mercury systolic and 84 diastolic; cervical, inguinal and axillary lymph nodes moderately enlarged and spleen markedly enlarged Laboratory work, performed before the youth came to the Clinic, disclosed "moderate anemia with poikilocytosis and anisocytosis, all white cell counts were between twenty and thirty thousand with normal differentials"

The history obtained when the youth was examined at the Clinic was essentially that furnished by the home physician The patient came alone and opportunity was not afforded to examine either parent. Physical findings corresponded with those reported by the home physician The palpable cervical, axillary and inguinal nodes were soft. The spleen extended below the umbilicus and well past the median line on the right. Laboratory findings were as follows

Urinalysis negative

Hemoglobin 9.3 gm per 100 c.c. of blood

Erythrocytes 3,340,000 per cu mm of blood

Leukocytes 14,500 per cu mm of blood

Differential leukocyte count, per cent lymphocytes, 26.0
monocytes, 10.0
neutrophils, 53.0
eosinophils, 9.0
basophils, 1.0
myelocytes, 1.0

Reticulocytes, per cent 20

Platelets 264,000 per cu mm of blood

Blood smear picture of congenital hemolytic icterus, with marked increase in regeneration, leukemoid reaction, with scattered myeloid immaturity of all forms back to the stem cell

Serum bilirubin indirect, 2.5 mg per 100 c.c.

Fragility of red blood cells, per cent patient, 0.50 to 0.38
control, 0.42 to 0.32

Sternal aspiration active marrow, with increase of normoblastic elements

Kline test for syphilis negative

Roentgenogram of thorax negative

A diagnosis of congenital hemolytic icterus was agreed on Splenectomy was performed without incident on December 1, 1942 Sixteen days later the blood findings were as follows

Hemoglobin 13.5 gm per 100 c.c. of blood

Red blood cells 4,200,000 per cu mm of blood

White blood cells 13,300 per cu mm of blood

Differential leukocyte count, per cent lymphocytes 27.5
monocytes, 5.0
neutrophils, 64.0
eosinophils, 2.5
basophils, 1.0

Platelets 570 000 per cu. mm. of blood

During the ensuing two years the patient remained well and was actively engaged in the aircraft industry. His referring physician kindly kept us informed of his progress and sent the following hematologic data

1 January 17 1944 —

Hemoglobin 105-110 per cent

Erythrocytes 5 630 000 per cu. mm. of blood

Leukocytes 24 000 per cu. mm. of blood

Differential leukocyte count, per cent lymphocytes 28.0
monocytes, 9.5
neutrophils 57.5
eosinophils, 4.5
basophils 0.5

2 October 10 1944 —

Hemoglobin 100-105 per cent

Erythrocytes 5 700 000 per cu. mm. of blood

Leukocytes 17,500 per cu. mm. of blood

Differential leukocyte count, per cent lymphocytes 23.0
monocytes, 14.0
neutrophils 59.5
eosinophils, 2.0
basophils 1.5

Discussion of Case 7—This case is interesting and not particularly typical. It is presented primarily because of the leukemoid reaction and the confusion with myelogenous leukemia which this caused. The difficulty here is that there was no family history of hemolytic icterus and that there was no opportunity to examine other members of the family for stigmas of the disease. The personal history, however, is suggestive of lifelong hemolytic activity and the large spleen would substantiate this. The laboratory findings are all compatible with the diagnosis, although the leukemoid reaction is out of proportion to the amount of regenerative activity (20 per cent reticulocytes). Such immaturity is usually found only in more acute crises. The characteristic blood smear, with its microcytic spherocytosis and evidence of increased regeneration, together with the increase in fragility, definitely influenced the decision to offer splenectomy. The postoperative course, with cessation of hemolytic activity, has fully justified this decision. The persistent leukocytosis may be a little disconcerting but leukocytosis after splenectomy is a common finding and probably indicates that some depressor control of the spleen has been removed.

CASE 8 Atypical Hemolytic Anemia.—A white housewife, thirty years of age, mother of one child, came to the Clinic complaining of varicose veins and pain in the left side. Two weeks before the patient had noticed some pain in the calf muscles of both legs while walking and she had consulted a "foot doctor" but without getting relief. She had some swelling of the feet at that time.

mm. of blood), increase in percentage of reticulocytes and continued evidence in the blood smear, of immaturity and active regeneration

It was decided to give transfusion one more trial in view of the partial relief afforded by the previous transfusions. During the next week four more transfusions of 500 c.c. each were given without unusual reaction. Although the value for hemoglobin rose to 9.6 gm per 100 c.c. of blood and erythrocytes numbered 3 620 000 per cubic millimeter of blood, leukocytes remained at 18,500 per cubic millimeter of blood, with reticulocytes at 30.6 per cent. All other evidence indicated that hemolysis continued to be active.

Splenectomy was accepted by the patient after the situation had been fully explained to her. She understood that possibly no relief would result.

On October 6, 1944, splenectomy was performed without incident. The liver, gallbladder and pelvic organs appeared normal. The spleen weighed 350 gm. One more transfusion was given postoperatively. The postoperative course was uneventful and, at the time of her dismissal, October 23, 1944, laboratory findings were:

Hemoglobin: 13.1 gm per 100 c.c. of blood

Erythrocytes: 4 730 000 per cu. mm. of blood

Leukocytes: 24 400 per cu. mm. of blood

Reticulocytes: per cent 4.4

Serum bilirubin: indirect, 1.0 mg per 100 c.c.

Fragility of erythrocytes: remained unchanged

The patient remained well and sent in the following report of studies of the blood made on December 28, 1944:

Hemoglobin: 95 per cent

Erythrocytes: 4,280 000 per cu. mm. of blood

Leukocytes: 6 900 per cu. mm. of blood

Discussion of Case 8—Here again is a case in which there was no family history of the disease under consideration and no previous personal history of hemolytic episodes. Moreover, the spleen was not remarkably enlarged. However, the patient had undergone evulsion of the left phrenic nerve for tuberculosis, a circumstance which would make splenomegaly more difficult to detect than if the operation had not been performed because, after such an operation, there is no diaphragmatic excursion to bring the spleen into the field of examination. The laboratory findings were those of congenital hemolytic icterus, although they could have been used to establish other diagnoses. It was felt that the condition might be Lederer's hemolytic anemia but repeated transfusions failed to halt the process. In view of the typical laboratory findings, splenectomy was offered. Prognosis was qualified, however, because of the lack of a family history of the disease and lack of a previous personal history of hemolytic activity. The response to splenectomy, however, indicates that this was an obscure case of congenital hemolytic icterus and not an atypical or "acquired" type of the disease.

CASE 9 Lederer's Anemia—The patient was a white man, fifty-four years of age, a hardware merchant. His family history, so far as could be ascertained, was irrelevant, although three of ten siblings had died of an unknown cause.

and one of the patient's six children had died of convulsions at the age of two years. A history of anemia, jaundice or blood dyscrasia was not obtained.

The patient was first seen at the Clinic in 1911 because of mild, reactive depression, in 1914, he returned because of a urinary infection. Thereafter, he had exacerbations of this urinary infection. In 1921, right otitis media required myringotomy and medical treatment. There were no complications, although the urinary infection was still present. An acutely purulent appendix was removed in 1924 without sequelae. In 1933, the patient returned with herpes of the right auricle.

On November 28, 1938, the patient again returned because of increasing urinary difficulty during the previous five years. This had been characterized by dysuria, frequency, nocturia and mild obstructive symptoms associated with infrequent attacks of severe renal colic. Persistent pyuria had been observed by the home physician.

Physical examination revealed that the man was robust and that he weighed 227 pounds (103 kg). The blood pressure was 112 mm of mercury systolic and 70 diastolic, temperature, pulse and respiration were normal. Results of examination of the head, nose, throat, thorax and abdomen were essentially negative. The prostate gland was slightly enlarged, as determined by rectal examination. Mild pyuria was noted. Results of laboratory examination were as follows:

Blood urea 26 mg per 100 c.c.
Hemoglobin 15 gm per 100 c.c. of blood
Leukocytes 6,000 per cu. mm of blood
Erythrocytes 4,700,000 per cu. mm of blood
Kline test for syphilis negative

Roentgenographic studies of the urinary tract made after intravenous injection of neo-ropax (disodium salt of *n*-methyl-3,5-diortho-4-pyridoxyl-2,6-dicarboxylic acid) showed the left kidney to be malrotated and hydronephrotic but with fair function remaining. It contained stony material, measuring 2 by 1.5 cm., in the tip of the lower calyx and probably a minute stone in the cortex. In the right ureter, 2 cm. above the bladder, there was a stone measuring 1 by 0.7 cm., with moderate dilation immediately above it, but otherwise the right kidney was normal.

The patient was advised to undergo manipulation and extraction of the right ureteral calculus, followed at a later date by exploration and removal of the stone from the left kidney. Accordingly, on December 12, under intravenous pentothal sodium anesthesia, the stone in the right ureter was engaged with the Council stone extractor. The next day, under the same type of anesthesia, the extractor was withdrawn but failed to dislodge the stone. After several attempts the stone was then removed with the Johnson stone extractor. There were no untoward reactions following these procedures and, on December 17, 1938, five days after admission, the patient was dismissed to his home in satisfactory condition.

Three days later he experienced abdominal distress, with nausea and vomiting followed by jaundice. He returned to the Clinic on December 23. He was definitely jaundiced but complained of nothing else. No drugs, other than the anesthetic agent, had been administered during this entire period. A preliminary diagnosis of intrahepatic jaundice was made and intravenous injection of glucose was started. Within the next few hours there was marked increase in the jaundice, profound prostration, fever and tachycardia. Laboratory examination yielded the following results:

Serum bilirubin direct, 15.4 mg per 100 c.c.
Blood urea 104 mg per 100 c.c.

Leukocytes 30,200 per cu mm of blood
 Hemoglobin 51 gm per 100 c.c. of blood
 Erythrocytes 1 880 000 per cu mm of blood
 Reticulated erythrocytes per cent 17.8
 Urinalysis albumin grade 4 (pus)
 Urine culture *Escherichia coli*
 Blood culture negative in forty-eight hours
 Fragility of erythrocytes per cent

Dec 26 1938

patient, 0.48 to 0.80

control, 0.44 to 0.32

Dec. 30 1938

patient, 0.42 to 0.28

control, 0.44 to 0.34

It became obvious in the few hours since he had left home that the patient was in a state of acute hemolytic crisis. Examination of blood smears disclosed a remarkable picture of phagocytosis and destruction of red blood cells occurring in the peripheral blood. There was anisocytosis, with considerable increase in regeneration but not the generalized spherical microcytosis of the red cells seen in familial hemolytic icterus, although some microcytes were present. Monocytes, macrophages and neutrophilic polymorphonuclear leukocytes were all engaged in this erythrophagocytic process.

The patient continued acutely ill, presenting a picture of shock cyanosis fever (104° F) tachycardia (140) and respiration 30 to 40 per minute. He was placed in oxygen and transfusion of 500 c.c. of citrated blood followed by 500 c.c. of 20 per cent solution of glucose, was given daily. Within twenty-four hours the erythrophagocytosis had ceased and within five days the number of leukocytes had fallen to normal levels and the erythrocyte count and values for hemoglobin were appreciably rising. Liver extract was administered parenterally for six days and iron by mouth for some time thereafter. On the twenty-eighth day after admission the following determinations were made:

Hemoglobin 12.3 gm per 100 cc. of blood

Erythrocytes 4 090 000 per cu mm. of blood

Leukocytes 6 700 per cu mm. of blood

Blood smears: essentially normal

The patient's recovery was delayed by the development of bronchopneumonia of low grade in the base of the right lung which necessitated a stay in hospital of fourteen days after the blood had returned to normal. No chemotherapy was used in treating the pneumonia in view of this recent blood crisis. From the time of the clinical improvement, which started after the first transfusion, evidence of renal damage began to disappear: the albumin had completely disappeared from the urine and the blood urea had returned to normal limits by the time of dismissal. At the end of the first twenty four hours of treatment, the value for serum bilirubin which had been 15.4 per 100 c.c. at the height of the crisis, had dropped to 10.7 with associated clearing of the jaundice. On the fourth day of treatment the value for serum bilirubin was 4.1 and on the sixth day 2.0 on the ninth day it was 1 mg per 100 c.c. The direct van den Bergh reaction however persisted for several days. After recovery the patient was sent home at which time his only treatment consisted of administration of iron. He returned to the Clinic one month after dismissal and laboratory examinations gave the following results:

Erythrocytes 4 610 000 per cu. mm of blood

Leukocytes 8 000 per cu mm of blood

Blood smear normal

The patient was in good health except for persistence of dysuria and moderate pyuria.

In November 1939 he returned to the Clinic for left pelvic lithotomy which

was performed on November 20, 1939 Postoperative convalescence was again delayed because of the development of postoperative pneumonia in the right lung, which proved to be a Type XXIII pneumococcic pneumonia In view of the fact that the blood was entirely normal except for mild leukocytosis (14,300 per cubic millimeter of blood) associated with the pneumonia, the patient was given sulfapyridine by mouth for four and a half days and made an excellent recovery He remained well

Discussion of Case 9—This case illustrates an acute hemolytic process associated with an infection, that is, acute Lederer's anemia Here then was no previous history of hemolysis and the entire picture was one of an acute process The fragility of the red blood cells was essentially normal and spherocytosis was not outstanding on examination of the blood smear The prompt response to transfusion, without recurrence, is final proof that this represents a case of Lederer's anemia

CASE 10 Acute Hemolytic Anemia Dependent on Rh Factor—A married white woman, twenty-nine years of age, was admitted to the hospital by ambulance, acutely ill with "anemia and jaundice"

Ten years before, she had undergone cholecystectomy elsewhere for gangrenous cholecystitis Jaundice, nausea and vomiting had been present before the operation

Following cholecystectomy, she had remained relatively well until two months before admission, when she had noted dyspnea on exertion, tachycardia, throbbing temporal pulsations and other symptoms of severe anemia She was given large doses of liver extract and then was hospitalized for transfusions According to her history, she had improved on this regimen, the concentration of hemoglobin rose to 60 per cent and she felt much better Administration of liver extract was continued, but without transfusions, and she again had become anemic Further transfusions had been given but reactions had become more frequent and severe and were accompanied by oliguria, passage of dark brown urine, jaundice, chills and fever The relationship of the jaundice in time, to the transfusions, was not definitely clear in the history There had followed again a period of improvement for no known reason but, two weeks before admission to the Clinic, another severe relapse had occurred Reactions to transfusions had become very severe and, in spite of her receiving blood every other day, she had become progressively more anemic

On physical examination at the Clinic the patient was found to be very dyspneic and anxious Her skin was jaundiced and the mucous membranes were very pale She was moderately dehydrated The spleen extended below and to the right of the umbilicus, while the edge of the liver was down nearly to the same level Both organs were tender Laboratory findings were as follows

Urinalysis essentially negative

Hemoglobin 4.7 gm per 100 cc of blood

Erythrocytes 1,300,000 per cu mm of blood

Leukocytes 11,600 per cu mm of blood

Blood smear hypochromic microcytic anemia, with marked increased regeneration, some spherocytes, scattered myeloid immaturity of all forms back to the stem cell, with normoblasts, many abnormal large lymphocytes with immature nucleus pattern

Fragility of red blood cells normal

Kline test for syphilis negative

Serum bilirubin direct 12.9 mg per 100 c.c.
indirect, 2.5 mg per 100 c.c.

Blood urea 26 mg per 100 c.c.

Serum proteins 7.8 mg. per 100 c.c.

Albumin globulin ratio 1/1.24

Prothrombin time 23 sec. (normal, 18)

Blood group 0

Rh factor Rh negative with anti Rh agglutinins present in serum

Because of the patient's extreme anemia and dehydration she was given solution of glucose intravenously, and a transfusion of 500 c.c. of Rh negative blood. She experienced no reaction. The next day another transfusion of Rh negative blood was started but a reaction characterized by chilliness, urticaria and asthma developed so that it was discontinued. The hemoglobin now was 2.6 gm. per 100 c.c. of blood and the jaundice was deepening and taking on a definite green tinge (biliverdinemia). Bile now appeared in the urine. The jaundice rapidly deepened, the patient went into a coma and died four days after admission. Permission to perform necropsy was refused.

Discussion of Case 10—This case probably represents a type of hemolytic disease that is secondary to transfusions of incompatible blood as determined by the Rh factor. What this patient's underlying disease was is not known, it might well have been cirrhosis of the liver with secondary congestive splenomegaly, since her final course indicated hepatic failure. However, the acute hemolytic phase probably was due to her Rh negativity, with the development of specific Rh agglutinins following the multiple transfusions of blood of unknown Rh type. In any such case in which multiple transfusions are given, the Rh factor should be determined and if an Rh negative test results, only Rh negative blood can be used. Hemolytic crises will follow repeated transfusions of Rh positive blood.

Idiopathic Thrombocytopenic Purpura.—This disease may be either chronic or acute and the chronic form may become acute periodically. It is manifested by a tendency to bleeding and usually there are petechiae or ecchymotic spots in the skin. Depending on the severity of the disease, bleeding may take place from any mucous membrane or into any organ and, most dangerously, into the brain or its coverings. This last is not uncommonly the cause of death and one of the most important reasons for early and accurate diagnosis.

The disease is fundamentally due to lack of blood platelets. The platelets may be destroyed by the spleen or formation of platelets may be suppressed by some splenic action. This point is still debated. Sternal aspiration however, usually discloses the presence of plenty of megakaryocytes and many young forms may be present. The other bone marrow elements are normal unless formation of red cells is increased due to hemorrhage.

Sternal aspiration often is necessary to distinguish acute leukopenic leukemia or aleukemic leukemia from thrombocytopenic purpura. Thrombocytopenic purpura may be part of an aplastic anemia, in which case all bone marrow elements are reduced. Splenomegaly, unless an acute exacerbation is in progress, seldom is present in this disease and, when it is present, should arouse suspicion of primary leukemia or other disease which may cause thrombocytopenia, however, in the chronic case, splenomegaly may be present as part of the syndrome.

The diagnosis is made from the history of purpura, the objective evidence of purpura, a low platelet count, a prolonged bleeding time and lack of clot retraction. Coagulation time is not disturbed but, as stated, the clot does not retract after formation but makes a soft, jelly-like mass. There should be no disturbance in red or white cell counts unless anemia or leukocytosis results from hemorrhage or intercurrent infection. In severe hemorrhage, however, there may be marked anemia and leukocytosis with a leukemoid reaction, which often raises the question of whether the condition at hand is leukopenic myelogenous leukemia. The tourniquet test is positive.

It should be stressed that occasionally thrombocytopenic purpura is secondary to acute infections, particularly diseases of childhood. The patients usually have a spontaneous remission following disappearance of the primary infection if they are supported with transfusions during the acute phase.

Sternal aspiration should be performed on these patients to rule out leukopenic leukemia as well as to determine the presence or absence of megakaryocytes before considering splenectomy.

CASE 11. *Acute Thrombocytopenic Purpura*—A white girl, ten years of age, was brought to a hospital in Rochester by ambulance and was admitted in a state of shock from loss of blood. She was bleeding profusely from the gums and nose. She vomited blood after admission to her room and had been passing blood in her urine and from her bowels. She was covered with purpuric spots and petechiae. Her pulse was extremely rapid and thready and her blood pressure could not be obtained. She was exceedingly thirsty, had air hunger and gave all other evidences of hemorrhage. A transfusion was started immediately and 1,000 c.c. of blood was given in the next few hours without reaction. The girl began to come out of her state of shock and, with the administration of a small dose of morphine, she was soon asleep.

The past history, obtained from the mother, disclosed nothing remarkable. As for the condition at hand, the child had been well until a few weeks before onset of the episode for which she had been brought to the Clinic. About two weeks before her admission, she had had a few bruises on the extremities and after she had wept petechiae had appeared about the eyelids, where she had rubbed them. A few days before the acute onset, her mother had noticed, on her pillow, some blood that had oozed from her gums during the night. She next had begun to have nosebleeds and, due to the severity of the nosebleeds

and the bleeding from the gums as well as because of the presence of extensive ecchymosis and petechiae she had been admitted to a hospital near her home. There her course in the next forty-eight hours had become rapidly worse and gastro-intestinal and renal bleeding had begun. She had been given a transfusion of blood and had been sent to Rochester.

Physical examination except for the widespread bleeding and a palpable spleen, did not reveal anything remarkable. Albumin and red blood cells were found in the urine. The concentration of hemoglobin in the blood was not determined. Examination of the blood gave the following results:

Erythrocytes: 1 690 000 per cu. mm. of blood

Leukocytes 48 100 per cu. mm. of blood

Platelets 33 000 per cu. mm. of blood

Reticulocytes per cent 19

Bleeding time 12 minutes

Blood smear marked regeneration with normoblasts leukocytosis with myeloid immaturity of all forms back to the stem cell, no platelets seen

Due to the critical condition of the patient she received 1,000 c.c. of blood on admission. For these reasons other confirmatory laboratory examinations such as coagulation time, clot retraction time, sternal aspiration and prothrombin time, were not performed.

A diagnosis of acute thrombocytopenic purpura was made and with the full effect of the transfusion of 1 000 c.c. of blood controlling her bleeding splenectomy was performed as an emergency operation. Her postoperative course was remarkably free of any complications: all bleeding ceased and the number of her platelets gradually rose to normal in the following three weeks. The rise in the number of platelets was much slower than had been expected but, during the ensuing five years, she remained perfectly well without any recurrence. When seen last year for tonsillectomy her platelets numbered 210 000 per cubic millimeter of blood and bleeding time was three minutes thirty seconds. All other blood values were normal and laboratory tests and physical examination gave negative results.

Discussion of Case II—While this case presented the typical picture of acute thrombocytopenic purpura, the possibility that acute leukemia was present had to be ruled out. Acute leukemias, most particularly the leukopenic type of the disease, are commonly mistaken for idiopathic thrombocytopenic purpura. The bleeding of acute leukemia is secondary to the thrombocytopenic purpura which accompanies the acute leukemic process. Lack of peripheral adenopathy, as well as lack of any history previous to the hemorrhagic phenomena, were in favor of purpura. The leukocytosis with the evidence of immaturity which was present, was confusing but was entirely compatible with copious hemorrhage and was an expression of the regenerative activity of the bone marrow. The reticulocyte count was further evidence of the same while the anemia was secondary to hemorrhage. The classical findings of low number of platelets and prolonged bleeding time were present and if it had not been felt that the case constituted an emergency time could have been taken for coagulation and clot retraction studies.

and they would have been helpful, since clot retraction should have been absent if the condition was thrombocytopenic purpura. Again, if the condition had not been so acute, sternal aspiration would have been done further to rule out acute leukemia and to determine the presence or absence of megakaryocytes. The postoperative course, however, verified the diagnosis of acute thrombocytopenic purpura.

CASE 12 Chronic Thrombocytopenic Purpura With Acute Exacerbation—A white farmer, fifty-one years of age, first came to the Clinic in July, 1943. He complained of bleeding from the bowel and of loss of weight. A small rectal polyp was felt to be responsible for the loss of blood and it was fulgurized. The man had an exophthalmic goiter, with marked symptoms, and thyroidectomy was performed without incident.

The patient returned in December, 1943, for repair of a troublesome right inguinal hernia. Following operation, a hematoma developed in the wound. This was evacuated and the wound healed without further trouble.

Again, in June, 1944, the man came for re-examination of the rectum. There was no evidence of recurrence of the polyp. At the end of January, 1945, he was admitted to the hospital because severe purpura constituted an emergency condition. He was bleeding from the nose, gums and gastro-intestinal tract and lesions of severe purpura were found in the skin and conjunctiva. There were some neurologic findings and mental confusion to suggest subarachnoid bleeding.

In November, 1944, pain had developed in the head and investigation of the sinuses had been carried out elsewhere. The nose had continued to bleed for days afterwards and purpuric spots had begun to appear on the lower extremities. After a month of this type of trouble, the man had been hospitalized and transfusions had been given. During the month before he again returned to the Clinic, he had received twelve transfusions and had had some rather severe reactions. For several days he had vomited considerable blood and had had melena.

At the time of physical examination at the Clinic the man was rather confused mentally and much of his history, a significant part of which will be related subsequently, was obtained from his wife. There were conjunctival hemorrhages, large blood clots around the gums and in the nose and the skin was covered with purpuric spots and petechiae. On the shins was a brown pigmentation, which was the result of his bumping his shins with milk cans during previous years. It was now that there was elicited a history of easy bruising during most of the patient's adolescent and adult life, together with frequent epistaxis and occasional bleeding from the gums. On examination of the thorax, some râles were heard in both phases. The pulse was rapid but there was no bruit. The spleen extended to the left of the umbilicus, while the liver was easily palpated. Laboratory findings were as follows:

Urinalysis specific gravity, 1.022
albumin, grade 2
sugar, none
red blood cells, grade 3
pus, grade 1

Hemoglobin 8.0 gm per 100 c.c. of blood
Red blood cells 2,360,000 per cu. mm. of blood
Leukocytes 3,700 per cu. mm. of blood

Differential leukocyto count, per cent: lymphocytes 39
 monocytes 5
 neutrophils 54
 eosinophils 1
 basophils 1

Platelets 20 000 per cu mm of blood

Blood smear no platelets seen marked increase in regeneration; mild leukopenia

Bleeding time still bleeding at end of 30 minutes

Clot retraction no retraction in 16 hours

Blood group: A

Rh factor: positive

Blood urea 130 mg per 100 c.c.

Blood creatinine 6.7 mg per 100 c.c.

Serum bilirubin direct, 0

indirect, 1.3 mg per 100 c.c.

Sternal aspiration active bone marrow numerous megakaryocytes on the smear

Röntgenologic examination of the thorax gave negative results

A diagnosis of acute exacerbation of chronic thrombocytopenic purpura was made. Splenectomy was performed without untoward incident on the day after admission. The following day the white blood cell count had risen from the previous leukopenic levels to 30 000 per cubic millimeter of blood while the number of platelets had risen from 20 000 to 97 000 per cubic millimeter of blood. At the end of the next twenty four hours platelets numbered 284 000 with the blood counts otherwise remaining constant. The postoperative course was uneventful except for persistent elevation of the values for blood urea and blood creatinine. Even at the time of the patient's dismissal three weeks later the value for blood urea was 60 mg per 100 c.c. and that for blood creatinine was 3.6 mg per 100 c.c. As for the urine, the specific gravity ranged from 1.004 to 1.009 albumin of grade 2 was present and occasional red blood cells and casts were found. Following the peak value for platelets of 284 000 per cubic millimeter of blood, which appeared on the third postoperative day the platelet count gradually receded until, at the time of the patient's dismissal, it was 19 000 or approximately at the preoperative level. The man however was completely free of any hemorrhagic trouble.

Discussion of Case 12—It is interesting that this patient should have undergone major surgical operations without undue trouble on two occasions in the year preceding the acute exacerbation of chronic thrombocytopenic purpura. Until the acute condition arose, mention had not been made of a tendency to bleed and the patient had not thought that his recurring nosebleeds or the occasional bleeding of his gums was of significance. In view of the subsequent course, the marked pigmentation of his shins became significant. When he handled milk, his shins frequently were bumped with large milk cans and this always produced a large bruise, which subsequently faded but at the site, pigmentation became residual. This history and physical finding undoubtedly establish a diagnosis of previously benign chronic thrombocytopenic purpura. This case

also illustrates how severe an acute exacerbation of one of these seemingly benign, chronic conditions can be

The degree of anemia is adequately explained by the amount of blood lost but the fact of the leukopenia raised the question whether some other diseases might be in the background, particularly leukemia I believe, however, that the leukopenia is explained by the continual loss of leukocytes to the tissues, associated with the widespread hemorrhages, as well as by the splenic effect.

Laboratory findings otherwise fit in with the history, to establish a diagnosis of thrombocytopenic purpura, that is, low platelet count, prolonged bleeding time and lack of clot retraction

The degree of splenomegaly also was disconcerting but, considering that the acute phase had been present for at least two months, progressive splenic enlargement could be expected

Renal insufficiency may have been due to hemorrhage into the kidney and toxic nephritis secondary to numerous transfusions and transfusion reactions

Another interesting feature of this case is the immediate post-operative rise in the platelet count, followed by a progressive fall to preoperative levels, without hemorrhagic manifestations This is of common occurrence in the chronic case when splenectomy is performed but the therapeutic result makes splenectomy worth while in spite of the later values for platelets

Primary Splenic Neutropenia—Primary splenic neutropenia was described as a clinical entity by Wiseman and Doan,^{17 18} and, while the condition is not of common occurrence, it must be borne in mind in all cases in which splenomegaly and associated neutropenia are present There are some cases of so-called Banti's syndrome in which the leukopenia may be a prominent feature and undoubtedly there are some instances in which the two conditions meet on common ground In primary splenic neutropenia, the phagocytic activity of the spleen evidently is directed toward the neutrophils or else the spleen exerts a suppressive effect on the bone marrow Patients commonly present the symptoms of fatigue and recurring mild or severe septic states There is a chronic neutropenia, however, in times of acute exacerbation of the disease, neutrophils may be absent and all of the complicating sepsis, ulceration and prostration that go with this phenomenon may be evident The spleen enlarges at this time and may be tender The history of easy fatigability and recurring episodes of vague malaise and aching, as well as the history of acute episodes, is important Laboratory work will disclose distinct neutropenia or agranulocytosis, without evidence of immaturity or abnormalities of the other blood elements Sternal aspiration will reveal hyperplastic marrow, with essentially normal

dispersion of the myeloid elements, although there may be some shift to the left

The differentiation from acute leukemia with marked leukopenia presents the most difficult diagnostic problem. Careful examination of the blood smears in acute leukemia, however, would reveal that many of the reported lymphocytes in the differential count are actually stem cells and sternal aspiration should reveal a leukemic picture, with a majority of the cells again being stem cells. Commonly the lymph nodes are soft and tender in leukemia and hemorrhagic phenomena due to reduced numbers of platelets are present, while anemia is often a prominent characteristic.

Doan and Wright recently have pointed out that the spleen may exert destructive action on all elements of the blood or a suppressive action on the bone marrow, thus reducing the number of erythrocytes, platelets and granulocytes in the peripheral blood. The presence of this condition would tend to confuse the diagnosis of all forms of anemia, purpura and leukemia.

CASE 13 Primary Splenic Neutropenia.—A white woman sixty two years of age, was admitted to the Clinic in August 1942 complaining of weakness, a large spleen and a low white count. Splenomegaly had been found on routine physical examination elsewhere in 1922. Moderate leukopenia (3 000 to 5 000 white blood cells per cubic millimeter of blood) had been found on frequent re-examinations during the ensuing twenty years. She made no particular complaints other than that she fatigued easily.

In January 1942, she had had an acute illness. White blood cells then had numbered only 800 per cubic millimeter of blood and only 3 per cent were neutrophils. Symptoms were primarily referable to the upper part of the respiratory tract and there was a complicating otitis media. This course had continued for three weeks and the temperature had been 102 to 103 F. Treatment had consisted of two transfusions of blood and administration of pent nucleotide (sodium salts of the pentose nucleotides from the ribonucleic acid of yeast) and yellow bone marrow extract. There had been no associated anemia and no hemorrhagic phenomena. The number of white blood cells slowly had returned to around 3,500 per cubic millimeter of blood as the fever and infection had subsided. Fatigue and exhaustion had persisted to the time of admission, as had the neutropenia, with the number of white blood cells fluctuating, and descending as low as 800 per cubic millimeter of blood.

On examination the patient was found to be well developed and well nourished. She weighed 140 pounds (63.5 kg) and was not in acute distress. The abdomen was not easy to examine and whether some ascites was present was questionable. The spleen could be felt three or four finger breadths below the costal margin. Laboratory findings revealed

Hemoglobin 12.3 gm per 100 c.c. of blood

Erythrocytes 4 010 000 per cu mm of blood

Leukocytes 1,500 per cu mm of blood

Differential leukocyte count per cent lymphocytes 81.0

monocytes 18.0

neutrophils 19.0

eosinophils 1.0

basophils 1.0

Platelets 51,000 per cu mm of blood

Reticulocytes, per cent 2.7

Blood smears some microcytosis in addition to the neutropenia, no immaturity, some toxic granulation of the neutrophils

Sternal aspiration essentially normal marrow except for some shift to the left in the myeloid line and toxic changes, megakaryocytes not seen in the preparation

Liver function test (bromsulfalein) dye retention, grade 2

Serum bilirubin indirect, 1.2 mg per 100 c.c.

Splenectomy was performed on September 4, at which time some evidence of hepatitis was found and a specimen for biopsy was taken from the liver. In addition to a large spleen (900 gm.), one accessory spleen was found. The pathologist's report on the hepatic tissue read, "chronic hepatitis with fatty degeneration." In the afternoon of the day on which splenectomy was performed, the patient's white blood cells numbered 7,600 per cubic millimeter of blood. The next day (September 5) results of examination of the blood were as follows:

Red blood cells 2,900,000 per cu mm of blood

White blood cells 9,000 per cu mm of blood

Differential leukocyte count, per cent neutrophils, 73.5

Platelets 209,000 per cu mm of blood

Except for mild, left diaphragmatic pleurisy with effusion, the postoperative course was uncomplicated. The number of white blood cells ranged upward to 15,000 per cubic millimeter of blood and the platelets to 350,000.

The patient remained well and blood values, determined elsewhere on January 4, 1944, were normal, as follows:

Hemoglobin 85 per cent

Erythrocytes 4,730,000 per cu mm of blood

Leukocytes 7,650 per cu mm of blood

Differential leukocyte count normal

Discussion of Case 13—This case was not clear-cut but splenectomy gave a good therapeutic result. There is much here in favor of a diagnosis of congestive splenomegaly secondary to low grade cirrhosis of the liver. The relevant findings are the retention of dye, grade 2, on liver function test and the questionable ascites (not found at the time of surgical operation). The history of splenomegaly being present for twenty years is against the existence of any active cirrhotic process, unless a "burnt-out" process is assumed to have been present along with residual splenomegaly. At all events, the outstanding feature is splenic activity with a persistent leukopenia which eventually produced agranulocytic episodes. Also, mild thrombocytopenia was associated with the leukopenia, although purpura never was evident. Chronic splenomegaly of long standing is not an uncommon occurrence in association with congenital hemolytic anemia and it might be expected to be found in the presence of chronic splenic neutropenia. The diagnosis is adequately supported by the peripheral neutropenia, the hyperplastic bone marrow and the history of recurring agranulocytosis. The return of the peripheral blood picture to normal would seem defi-

nately to establish the conclusion that the splenomegaly was responsible for the previous chronic neutropenia

CONGESTIVE FORMS OF SPLENOMEGALY

Congestive Splenomegaly (Banti's Syndrome; Splenic Anemia)—There has been controversy over this syndrome since study of it was initiated by Banti in 1883. Not only has the etiology of the syndrome been disputed, but its actual existence has been challenged. It is rather poorly defined and probably includes several entities which may eventually be established as independent syndromes, for instance, (1) cirrhosis of the liver with splenomegaly, (2) abdominal thrombophlebitis particularly thrombophlebitis of the splenic vein, (3) splenomegaly secondary to venous obstruction by extrinsic causes, (4) chronic infectious splenomegaly and so on. The term "congestive splenomegaly" has been offered for this syndrome since there is much evidence to suggest that a chronic obstructing lesion at the portal or splenic vein is responsible for the enlargement of the spleen.^{9 10 12 14 15} In the presence of progressive splenomegaly of long standing, it is not difficult to consider the variable blood finding (anemia, leukopenia and thrombocytopenia) as a tertiary phenomenon dependent on the splenomegaly and not necessarily on the original pathologic change. At all events, the congestive hypothesis gives a good working basis for differential diagnosis.

This condition originally was described as affecting young individuals. It was considered to be due to an unknown toxin which produced splenomegaly and cirrhosis of the liver, the cirrhosis being the cause of eventual death if the patient did not succumb to hemorrhage from his varices first.

Many workers now believe that if cirrhosis is not part of the original pathologic condition it does not necessarily develop. If congestive splenomegaly is to be explained from an anatomic standpoint, the cirrhosis of the liver should occur first and the hepatic condition should give rise to chronic obstruction of the portal vein and secondary splenomegaly. If the splenic vein becomes obstructed by external pressure or intrinsic thrombophlebitis, the obstruction to the flow of blood will produce chronic passive congestion of the spleen and will result in progressive enlargement of this organ. It can also be seen, with such obstruction why varicosities of the esophagus develop by a shunting of the circulation away from the portal vein and up through the gastric and esophageal vessels to the superior vena cava (fig. 116).

The findings in the peripheral blood undoubtedly are secondary to the splenomegaly, although the nature of this is not clear. In

the majority of the cases there is some disturbance in the values for any or all of the bone marrow elements in the circulating blood. In so-called splenic anemia, when present, ordinarily there is no evidence of hemolytic activity of the spleen. The anemia may be normocytic and normochromic, suggesting suppressed bone marrow activity or, in some cases, particularly if cirrhosis of the liver is an outstanding feature, macrocytosis may be present. In cases in which repeated hemorrhage takes place, microcytic hypochromic anemia of the non deficiency type can be expected. Commonly there is a neutropenia, which again may reflect increased phagocytic activity of the spleen or some suppressive effect on the bone marrow. The same can be said for the thrombocytopenia.

Following splenectomy, the blood values usually return to more nearly normal levels and this, I believe, is the greatest indication for splenectomy in this disease. A secondary benefit is that the blood which formerly went to and from the spleen is eliminated and thus reduces the load on the collateral circulation. However, there is usually no diminution in size of the patient's varicosities and hemorrhage usually will recur. If the congestive or obstructive hypothesis is correct, the above could be expected, since splenectomy in no way alters the circulatory bed itself. If cirrhosis of the liver is primary, there is probably little to expect from splenectomy other than correction of the blood values which may be secondary to the splenomegaly. It would not be expected that the cirrhotic process would be altered and, if cirrhosis is present, treatment should be that used for primary cirrhosis of the liver.

In the differential diagnosis of this condition, liver function tests should be employed. In cases in which abdominal thrombophlebitis involving the portal or splenic vein or both is present, there is often a history of recurring bouts of abdominal pain, leukocytosis and physical findings suggestive of an acute condition of the abdomen. Splenic infarctions are not of uncommon occurrence in association with this condition and they may be extensive, giving rise to a splenic abscess. This rather poorly defined syndrome often is diagnosed by excluding, one after another, the other forms of splenomegaly.

CASE 14 Abdominal Thrombophlebitis and Infectious Splenomegaly—A white housewife, twenty-seven years of age, was admitted to the Clinic in November, 1942. She complained that she had had recurrent attacks of abdominal pain for four years. The attacks were consistent in their manifestations and occurred at intervals of from one to five weeks. Each attack lasted from three to five days. Between attacks the patient was free of symptoms and considered herself in good health. An attack was characterized by fatigue of gradual onset and vague distress, which warned her that an attack was impending. The pain was described as heavy, constant, severe, aching, with occasional sharp, stab-

bing episodes and it would be felt over most of the abdomen with no point of localization that the patient could determine. There was always extreme abdominal tenderness and associated fever. During the first day or two, the woman was in constant agony and finally would be worn out from thrashing and writhing in bed. About the third day she would become nauseated and would start to vomit. Then the attack would wear off and the patient would go into a sleep of exhaustion after which she was well until the next attack. Practically no foods or liquids were taken during the attacks and the patient was unable to relate them to any type of food or to nervous tension. She had never been jaundiced, had not had shaking chills and the temperature never had been high. The fever may have been of a dehydration type. There had been no gastro-intestinal bleeding and no change in the stools. Swelling and urticaria had been absent. At the time of the patient's admission she was just getting over an attack. Appendectomy had been done elsewhere in July 1942, without altering the attacks.

Physical examination revealed that the patient was well developed and weighed 125 pounds (56.7 kg.). Blood pressures were 108 mm. of mercury systolic and 85 diastolic. The pulse rate was 108 per minute and the temperature, 99.4° F. The entire abdomen was tender and the patient was unable to relax well for examination. Definite, localized tenderness was not found. The spleen was easily palpable. The rest of the examination did not disclose anything remarkable. Another attack developed while the woman was being examined at the Clinic and she was hospitalized. Laboratory findings in November 1942 revealed the following:

Urinalysis: specific gravity 1.026
 reaction acid
 albumin, grade 1
 red blood cells grade 1
 pus grade 1

Second urinalysis: negative

Hemoglobin 8.3 to 7.4 gm. per 100 c.c. of blood

Erythrocytes 2,730,000 to 3,500,000 per cu. mm. of blood

Leukocytes 5,200 to 2,500 per cu. mm. of blood

Reticulocytes per cent 1.8 to 5.7

Platelets 38,000 to 63,000 per cu. mm. of blood

Bleeding time 6 minutes to 14 minutes and 35 seconds

Blood smear: hypochromasia, with considerable increase in regeneration
 some macrocytes moderate toxic changes in neutrophils reduced platelets

Serum bilirubin: indirect, 1.2 mg. per 100 c.c. of blood

Blood group B

Fragility of red blood cells normal

Sedimentation rate 46 mm. per hour (Westergren)

Blood urea: 28 mg. per 100 c.c.

Liver function test (bromsulphalein): no retention of dye

Two stools for occult blood: guaiac, negative
 benzidine, positive

Analysis of gastric content: total acidity 32
 free hydrochloric acid, 20
 quantity 80 c.c.

Roentgenograms of the thorax, gallbladder, stomach, esophagus (for varices), small bowel and colon gave negative results as did, also the excretory urogram.

It was believed that the woman probably had recurring abdominal thrombophlebitis and exploration, with splenectomy, in spite of its additional risk was advised if no other abdominal pathologic condition was found to account for the attacks. The woman elected not to undergo surgical operation at that time.

The patient returned in March, 1943, having had three or four attacks which had been more severe and of longer duration than those which she had experienced previously. There had been no other change in her condition and physical examination gave essentially the same results as those obtained on the previous visit. The spleen was very tender and extended 3 cm. below the costal margin. Laboratory findings were as follows:

Urinalysis negative

Hemoglobin 7.3 gm per 100 c.c. of blood

Erythrocytes 2,880,000 per cu. mm. of blood

Leukocytes 5,000 per cu. mm. of blood

Differential leukocyte count, per cent: lymphocytes, 11.5
monocytes, 6.0
neutrophils, 81.5
eosinophils, 1.0

Reticulocytes, per cent 3.7

Platelets 28,000 per cu. mm. of blood

Bleeding time 14 minutes and 40 seconds

Coagulation time 7 minutes

Sedimentation rate 35 mm. per hour

Blood smears hypochromic anemia with increased regeneration, regenerative macrocytes and toxic changes in neutrophils

Stools for occult blood guaiac, grade 4
benzidine, grade 4

Serum bilirubin indirect, 1.2 mg. per 100 c.c.

Abdominal exploration again was advised and this time the patient consented. At surgical operation the liver and spleen both were found to be enlarged but there was no other evidence suggestive of Banti's disease except slight engorgement of the vessels of the stomach. There were no adhesions about the spleen, no perisplenitis and no evidence of hepatic cirrhosis. The gastro-intestinal tract was entirely negative on exploration except for a portion of the upper part of the jejunum, starting approximately 6 inches (15.2 cm.) from the ligament of Treitz and extending downward for about 10 inches (25.4 cm.), where there was some localized, regional enteritis. The neighboring lymph nodes were markedly enlarged. The involved portion of the jejunum was resected well back into the normal portion of the intestine and end-to-end anastomosis was performed. The pathologist's report on the specimen was, "chronic purulent ulcerative jejunitis, with perijejunitis and inflammatory lymph nodes." The postoperative course was uneventful, although two transfusions were given because of anemia.

The patient again returned in October, 1943, stating that she had felt better during that summer than for a long time. In August, however, she had been found to be anemic, red blood cells numbered 3,000,000 per cubic millimeter of blood and the concentration of hemoglobin was reported as 46 per cent. Administration of iron and liver had been followed by improvement and, the week prior to her coming to the Clinic, she had started to complain of weakness and generalized abdominal pains, less severe than before. General physical examination gave essentially the same results as before, the spleen still extended a distance equivalent to three finger breadths below the costal margin. Laboratory findings were as follows:

Urinalysis specific gravity 1.030

reaction acid

albumin grade 2

Erythrocytes 4 050 000 per cu. mm. of blood

Leukocytes 8,200 per cu. mm. of blood

Blood smear hypochromic anemia with increased regeneration mild toxic changes in polymorphonuclears

Results of roentgenologic examination of the small bowel were reported as follows "No definite evidence of regional enteritis at this time. Large spleen."

Since no definite evidence of recurring enteritis could be found the woman was sent home on a regimen consisting of a special diet, hematinics and rest. She was directed to return in a few months for re-examination.

The patient was in the Clinic in April 1944 with her mother and reported that her previous trouble had not been progressive and that she had been feeling well for some months. She had gained some weight and her appetite was good. She returned again however in November 1944 complaining of malaise, weakness, anorexia and abdominal pain which was rather constant and was unrelated to meals. This pain occasionally was colicky in nature and there had been some vomiting. The spleen was about the same size as before and moderately tender. The edge of the liver also was palpable. The rest of her examination disclosed nothing remarkable. Laboratory findings were as follows:

Urinalysis negative

Hemoglobin 8.8 gm per 100 c.c. of blood

Erythrocytes 2,890 000 per cu. mm. of blood

Leukocytes 6 000 per cu. mm. of blood

Sedimentation rate 80 mm. per hour (Westergren)

Serum bilirubin indirect, 0.6 mg per 100 c.c.

Liver function no retention of dye

Stool positive for blood

Blood smear scattered macrocytes of regenerative type increased regeneration toxic changes in polymorphonuclears

Platelets appear reduced in number

Roentgenologic examinations disclosed the following: The colon and terminal portion of the ileum were negative; there was evidence of end-to-end jejunojejunostomy just beyond the ligament of Treitz, the small bowel otherwise was negative; the thorax was negative.

In view of the findings in the past, together with the splenic enlargement, abdominal exploration was made again on November 22, 1944. The scar of the previous operation was excised and the omentum was found to be markedly adherent to the incision. The wound was vascular and it was thought that colateral circulation was developing from the omentum to the abdominal wall. The spleen was definitely larger than it had been at the time of the previous operation. There were adhesions about it and perisplenitis. Also the veins over the stomach were dilated and those in the splenic pedicle were tremendously dilated. The liver was somewhat enlarged but otherwise appeared normal. Abdominal exploration gave no other positive results and there was no evidence of recurrence of the enteritis. Splenectomy was performed in the usual manner and the postoperative course was not remarkable in any way. Laboratory findings were as follows:

Hemoglobin 10.15 gm per 100 c.c.

Erythrocytes 3 660 000 per cu. mm. of blood

Leukocytes 5 400 per cu. mm. of blood

Platelets 225 000 per cu. mm. of blood

The patient has remained well.

Discussion of Case 14—This case illustrates not only the difficulty of diagnosing some types of splenomegaly but also the acute nature of some of the abdominal manifestations. Not only did this patient have attacks suggestive of an acute condition within the abdomen but studies of her blood reflected her splenic dysfunction. The hypochromic anemia could well have been secondary to loss of blood, particularly considering the increase in reticulocytes. Examination of two stools for occult blood gave negative results but the reports might well have been positive if repeated examinations had been made. Leukopenia as well as thrombocytopenia was present and the red cell count was low, that is, all bone marrow elements were reduced in number. Lengthening of the bleeding time probably was the result of a combination of a reduced number of platelets as well as of change in prothrombin time. The toxic change in the polymorphonuclear leukocytes is suggestive of an infectious process in this case, while the elevated sedimentation rate also favors such a diagnosis, probably both were due to involvement of the bowel even though only a small portion was affected. The examinations of stools and roentgenologic examinations were not helpful and this case illustrates the wisdom of exploration when clinical findings and history indicate it in spite of the lack of certain substantiating laboratory findings.

The history of this patient's recurring attacks of abdominal pain is interesting and, probably because of the high position of her enteritis, the history did not include mention of the periumbilical distribution of the pain which is characteristic of pain caused by a lesion of the small bowel. At the time of exploration, although the spleen was enlarged, there was little vascular evidence of circulatory disturbance and the splenomegaly could well have been on the basis of infection secondary to jejunitis. In spite of the fact that the diseased portion of the bowel was excised, the patient's symptoms recurred and, by the time of her second operation, a marked change had occurred in the spleen and its vascular supply. These changes constituted evidence of obstruction of the portal system, namely, considerable engorgement of the splenic vessels, increase in the size of the spleen and perisplenitis. The question presents itself whether, in this case, regional ileitis gave rise to secondary abdominal thrombophlebitis, with resulting congestive splenomegaly, or whether, actually, the following sequence was present: primary abdominal thrombophlebitis involving the mesenteric vessels with resulting changes in the bowel, spread of the thrombophlebitis into the splenic vein, finally, congestive splenomegaly.

It is unusual, in these cases of abdominal thrombophlebitis, to encounter as many severe, recurring abdominal episodes as took

place in this case. They are a feature of the disease however, and always should be sought for in the history. The blood findings were largely reflections of the splenomegaly and not characteristic of any one type of splenomegaly. The toxic changes favored the idea that an infectious process was present as did, of course, the acute nature of the attacks. However, in spite of extensive study, a definite diagnosis of abdominal thrombophlebitis was not established until the time of exploration.

Although the patient became well, only time will tell whether she will have further acute episodes due to progression of her primary disease. The splenectomy has corrected her blood picture.

CASE 15 Cirrhosis With Splenomegaly—This white housewife, forty-three years of age, came to the Clinic on March 20, 1945, with a history of having experienced gastric hemorrhages in January of the same year. After two weeks of melena she had entered a hospital. She had been on a regimen for ulcer during this acute episode and following it. The patient complained of bloating after eating and in the year previous to that of her visit to the Clinic, stools had been somewhat loose and watery. She had been troubled by some nausea in the morning at times.

Physical examination disclosed that the woman was well developed and well nourished but that her skin and sclera had a definitely icteric tinge. The liver was large, hard and irregular and the left lobe was prominent. The spleen extended a full handbreadth below the costal margin. Pelvic examination gave no evidence of the presence of masses in the cul-de-sac. Laboratory examinations revealed the following:

Urinalysis: negative (except for a trace of bile)

Hemoglobin: 11.6 gm per 100 c.c. of blood

Erythrocytes: 3,360,000 per cu. mm. of blood

Leukocytes: 1,700 per cu. mm. of blood

Differential leukocyte count, per cent: lymphocytes 31.0
monocytes, 7.0
neutrophils 57.0
eosinophils 4.0
basophils, 1.0

Platelets: 61,000 per cu. mm. of blood

Bleeding time: 11 minutes

Blood smear: leukopenia, anemia, thrombocytopenia, mild hypochromasia, no myeloid immaturity found

Kline test for syphilis: negative

Cholesterol: 201 mg per 100 c.c. of plasma

Cholesterol esters: 107 mg per 100 c.c. of plasma

Serum bilirubin: direct, 3.7 mg per 100 c.c.

indirect, 1.1 mg per 100 c.c.

Serum proteins: 5.6 gm per 100 c.c.

Albumin-globulin ratio: 1.7/1

Liver function test (bromsulfalein): retention of dye, grade 4

Sedimentation rate: 35 mm per hour (Westergren)

Prothrombin time: 22 seconds (normal 18 seconds)

Blood urea: 9 mg per 100 c.c.

Röntgenologic examinations disclosed the following: thorax, negative

stomach, distinct evidence of esophageal varices but otherwise negative, colon and terminal portion of ileum, negative

A clinical diagnosis of carcinoma of the liver or late cirrhosis of the liver was made. Peritoneoscopy disclosed cirrhosis of the liver with secondary enlargement of the spleen. The surgeon felt that the condition did not resemble Banti's syndrome, as there was no perisplenitis and there were no adhesions about the spleen. Evidence of malignancy was lacking. Biopsy of the liver resulted in a diagnosis of cirrhosis, grade 3. The patient was dismissed on a regimen for hepatic disease.

Discussion of Case 15—In contrast to the case of abdominal thrombophlebitis (Case 14), in Case 15 the patient made no complaints before her advanced cirrhosis produced physiologic changes which were noticeable to her and her family. Abdominal crises or other episodes had not occurred to draw the patient's attention to the pathologic condition which was developing. Her vague dyspepsia and intolerance of fatty foods was suggestive of hepatic disease. At the time of her examination, the anemia and leukopenia, thrombocytopenia and elevated bleeding time were reflections of her splenic dysfunction. The slight elevation of her prothrombin time may also have been a factor in her elevated bleeding time. Coagulation time was not determined but, in hepatic disease of this kind, with elevation of the prothrombin time, both bleeding time and coagulation time are prolonged, this is in contrast to thrombocytopenic purpura, wherein coagulation time is normal and bleeding time is elevated. The tremendously large, irregular liver, which had not given rise to complaint, together with the laboratory findings, suggested that a malignant growth of the liver was present. However, the true nature of the process was demonstrated by peritoneoscopy without great discomfort to the patient.

CASE 16 Metastatic Carcinoma of the Liver—A white female nurse, forty-seven years of age, was admitted to hospital because of extreme weakness and exhaustion, and with a diagnosis of hepatosplenomegaly. Her history was meager, and did not include mention of previous episodes of trouble. Until a few months before she came to the Clinic she had not felt "up to par" but the only definite complaints she had made were of some aching in the upper part of the abdomen, some chills, night sweats and a temperature which had reached 101° F. She had been examined at that time, a large liver and spleen had been found and she had been referred to the Clinic for further investigation. In the last month before her admission she had become so weak as to take to her bed. Anorexia was a prominent feature and there had been some nausea. She had not used drugs or chemicals which might account for hepatic cirrhosis.

On physical examination, the liver was found to be large, somewhat irregular and very hard, the left lobe was prominent. The spleen was enlarged and the umbilicus very firm. Pelvic examination did not disclose anything remarkable. Laboratory findings were as follows:

Urinalysis negative

Hemoglobin 11.9 gm per 100 c.c. of blood

Erythrocytes 4,090 000 per cu mm. of blood

Leukocytes 6700 per cu mm of blood

Blood smears some anisocytosis and increase in regeneration most of the neutrophils of the band form no immaturity

Platelets seemed normal

Kline test for syphilis negative

Serum bilirubin direct, negative

indirect 0.25 mg per 100 c.c.

Serum protein 7.0 mg per 100 c.c.

Albumin globulin ratio 17/1

Prothrombin time (Quick) 22 seconds (average normal 18 seconds)

Sedimentation rate 56 mm per hour (Westergren)

Liver function (bromsulfalein) retention of dye grade 4

Roentgenologic examination of the thorax esophagus and stomach gave negative results.

Definite diagnosis could not be established by ordinary methods and peritoneoscopy was performed. The liver was seen to be enlarged and appeared to be the site of a metastatic lesion. The pathologist reported that the specimen of liver removed for biopsy was the site of adenocarcinoma grade 2 probably metastatic from the colon.

Discussion of Case 16—A definite diagnosis possibly could have been established by means of roentgenologic examination of the colon, although there was no history to suggest the presence of such a lesion. The presenting hepatic tumor could have been attributable to cirrhosis of the liver, with secondary splenomegaly. However, the patient had had difficulty for only a short time and both organs were enormously enlarged. This favored a diagnosis of carcinoma although, in Case 15, in which cirrhosis of the liver and splenomegaly were present, the course was equally short and the history equally negative. The increased sedimentation rate is not outstanding and could be part of a cirrhotic or of a malignant process. As a piece of evidence it is rather against the presence of lymphoblastoma. The hematologic findings were not at all helpful although, with advanced cirrhosis, more severe anemia might be expected probably of the macrocytic type.

SPLENITIS

The most commonly occurring cause of splenomegaly is infectious splenitis. In the presence of acute infections the splenomegaly that results from the associated acute splenitis does not present a diagnostic problem. Chronic splenitis however such as may be associated with chronic malaria, mycotic infection tuberculosis, syphilis or brucellosis may present a difficult problem. The spleen may be enormous. Neither history nor examination may help to identify the primary disease. In such cases there may be secondary splenic effects on the hematopoietic system with resulting anemia leuko

penia or thrombocytopenia further to confuse the issue. In such cases, splenectomy usually is followed by reversion of the blood picture to normal^{5,6}. Splenectomy, of course, has further beneficial effect in cases in which the infection is still active for it removes a focus of offending organisms.

Brucellosis

CASE 17 *Brucellosis with Splenitis*—For eighteen months a white, male veterinarian, thirty-seven years of age, had been suffering from a progressive, debilitating, febrile disease. For a long time all diagnostic procedures had failed and he had been treated symptomatically with blood transfusions, penicillin, diet, pyridoxine (vitamin B₆) and other supportive measures. During this period his liver and spleen had progressively enlarged, his recurring bouts of fever had become more severe and his weight had declined from 225 pounds (102 kg) to 160 pounds (72.6 kg). Moderate anemia had been present, evidenced by a value for hemoglobin averaging around 10.5 gm per 100 c.c. of blood and a value for red blood cells of about 4,000,000 per cubic millimeter of blood. The leukopenia, of which counts of 2,000 to 3,000 white blood cells per cubic millimeter were evidence, had been persistent. Agglutination tests for brucellosis had been positive in a dilution of 1:80 before centrifuging and in a dilution of 1:320 after centrifuging.

The patient was convinced that he had brucellosis and asserted that on two occasions he had been inoculated accidentally with virulent organisms while vaccinating obstreperous calves. Blood cultures finally had proved the diagnosis and colonies of *Brucella* had developed on Hitchens medium kept at reduced oxygen tension. By agglutination tests, the strain of organisms with which the patient was infected had been shown to be the same as that used in the vaccine with which the patient had vaccinated cattle.

At this time the patient came to the Clinic for treatment with streptomycin. On admission to the hospital his face was flushed, his temperature was 101.2° F, the loss of weight he had sustained was evident, he was prostrated and hepatosplenomegaly was an outstanding feature. The spleen nearly filled the left side of the abdominal cavity. Laboratory findings were as follows:

Urinalysis specific gravity, 1.020
 albumin, grade 1
 red blood cells, grade 1
 pus, an occasional cell
 Hemoglobin 12.7 gm per 100 c.c. of blood
 Red blood cells 4,030,000 per cu. mm. of blood
 White blood cells 2,200 per cu. mm. of blood
 Differential leukocyte count, per cent lymphocytes, 66.0
 monocytes, 5.0
 neutrophils, 29.0

Reticulocytes, per cent 1.0

Platelets 127,000 per cu. mm. of blood

Blood smears neutropenia, with some toxic changes, some hypochromasia

Kline test for syphilis negative

Agglutination for *Brucella* positive at a dilution of 1:160

Blood cultures in brain broth and on blood agar negative

Blood cultures in tryptone broth positive for *Brucella* in eight days

Roentgenologic examination of the thorax gave negative results

In spite of the history and positive blood cultures I felt, as had other phys-

icians that the enormous splenomegaly, anemia, leukopenia and progressively downhill febrile course made lymphoblastoma, reticulo-endotheliosis or leukemia still possibilities.

Sternal aspiration was done but nothing more than toxic changes were present in the specimen of marrow.

Streptomycin 1 000 000 units per day was given intravenously. Treatment was tolerated well and there was a gratifying drop in temperature, improvement in appetite and gain in body weight. For two months repeated courses of streptomycin were given with excellent temporary results only to have the patient go into relapse soon after treatment had been discontinued. Splenectomy was then advised and accepted. At the time of surgical operation the spleen was found to extend downward to the iliac crest and moderate hepatitis was present. The spleen was removed with moderate difficulty and was found to weigh 2,700 gm.

The postoperative course in hospital during which the patient received streptomycin was uneventful except for daily fever. Thereafter for the six months that had elapsed when this report was written he remained perfectly well, regained his weight and strength and returned to work.

Discussion of Case 17—Confusion in this type of case arises from the marked splenomegaly of chronic splenitis occurring in the course of the disease that is primarily difficult to diagnose. In this case the presumptive diagnosis was correct but special techniques were required to prove it. I previously had encountered a case, not unlike Case 17 wherein agglutination tests made both in Rochester and elsewhere gave negative results, while in blood cultures (tryptose medium with reduced oxygen tension) colonies of *Brucella abortus* grew in due time.

The gratifying results of splenectomy in Case 17 suggest that this procedure might be employed more frequently and earlier in the course of the disease in other cases of chronic splenitis.

Subacute Bacterial Endocarditis—Splenomegaly is a common finding in the presence of subacute bacterial endocarditis. The infection, of course, usually is engrafted on the damaged valve of an old rheumatic heart or on residual embryonic structures in cases of congenital heart disease. The condition in the spleen is primarily infectious splenomegaly secondary to repeated lodging of infected emboli in the splenic substance. Because of the bacteremia proliferation of the reticulo-endothelial system takes place with the cells becoming actively phagocytic in the effort of the body to rid the blood stream of bacteria. One of the interesting hematologic findings that often will suggest the diagnosis in these cases is the presence of free phagocytic reticulo-endothelial cells in the blood smear. These cells have the characteristics of the reticulo-endothelial cells previously described, namely fine chromatin structure in sharp contrast to the parachromatin, clear-cut nuclear membrane and a variably large amount of cytoplasm usually containing

phagocytized debris. Although the diagnosis can be suspected from a clinical course of chills and fever, there are occasional cases in which the fever is minimal and there are rare cases in which a cardiac lesion cannot be demonstrated until late in the disease. In such cases, the finding of the characteristic phagocytic cells on the blood smear may be of considerable help and, if such cells are found, repeated blood cultures should be made until a positive culture is obtained. Occasionally, it is necessary to incubate these cultures long past the usual period in order to obtain a growth.

The blood findings, other than that of the characteristic phagocytic cell, usually are those of hypochromic anemia with increased regeneration, leukocytosis with variable toxic changes and elevated sedimentation rate. Embolic phenomena in the periphery of the body, particularly finger tips and joints, are commonly found and often are causes of complaint. In one case that I have encountered recently, however, the emboli were all in the pulmonary circulation and the repeated pulmonary episodes were the only thing of which the patient complained. Except for some roughening of the heart sounds in the tricuspid valve area, there were no cardiac findings. Examination of blood smears, however, revealed the characteristic phagocytic reticulo-endothelial cell and in every subsequent blood culture green-producing streptococci grew. It should be stressed that these phagocytic reticulo-endothelial cells often occur in showers and it may be necessary to make several blood smears, at different times, before they can be found, occasionally they are not found. Sometimes they are present in numbers in the first drop of blood taken from the lobe of the ear and are fewer or absent in succeeding drops.

CASE 18 Subacute Bacterial Endocarditis—A mother of two children, a white woman, twenty-eight years of age, came to the Clinic complaining of fatigue, exhaustion and red spots on her body. She had been having some fever and occasional mild chills. Approximately six months before her admission, in the course of her second pregnancy, she had had pleurisy. She had not felt well since her delivery.

On physical examination she was found to be anemic and her skin had a lemon yellow tinge. Her blood pressures were 100 mm of mercury systolic and 64 diastolic, her pulse rate was 112 per minute and her temperature, 100.8° F. A harsh systolic and diastolic murmur at the base of the heart was heard best to the left of the sternum, at the level of the fourth interspace. The spleen extended downward to the level of the umbilicus. There were scattered petechiae over the extremities and trunk. Laboratory findings were as follows:

Urinalysis specific gravity, 1.012
 albumin, grade 1
 hyaline and granular casts, occasional
 red blood cells, occasional
 pus, grade 1

Hemoglobin 7.8 gm per 100 cc of blood

Leukocytes 4 900 per cu mm of blood

Erythrocytes 3 180 000 per cu mm of blood

Blood smear marked toxic changes with an occasional phagocytic reticulo-endothelial cell

Kline test for syphilis negative

Blood urea 26 mg per 100 c.c.

Sedimentation rate 57 mm. per hour (Westergren)

Electrocardiogram rate 98 sinus tachycardia, slurred QRS complex in lead III QRS complex of low amplitude in leads I II and III, iso-electric T wave in lead III, notched P wave in lead II

Blood cultures green producing streptococci 120 colonies per c.c.

Röntgenologic examination of the thorax gave evidence of some cardiac enlargement, with pleuritic adhesions at the costophrenic angle

A diagnosis of subacute bacterial endocarditis probably on the basis of a congenital cardiac defect, was made Further study was advised with the possibility of surgical operation being offered, but the patient left the hospital.

Discussion of Case 18—In this, as many similar cases, the characteristic phagocytic reticulo endothelial cell was found before blood cultures were positive Such a finding was not of great help in this case but in more obscure cases it could be the one finding that might give the clue to the diagnosis

Histoplasmosis.—Although histoplasmosis is of relatively rare occurrence in man, its increasing incidence makes it well worthy of consideration in differential diagnosis in cases in which splenomegaly is a feature More cases of histoplasmosis are being reported yearly than before and the distribution of the disease is world wide Recent reviews by Parsons and Zarafonitis and Iams, Tenen and Flanagan including bibliographies, reports of cases and discussions should be perused by those interested in the disease

The offending organism in this disease is a yeastlike fungus which grows readily on most media, but most prolifically on media containing considerable protein (blood agar) In cultures at room temperatures, the fungus reverts to the mycelial forms while, at 37° C on tightly sealed blood agar slants, or when animals are inoculated with it the yeastlike form is preserved The characteristic feature of the organism is the tuberculate chlamydospore

The organism, *Histoplasma capsulatum* occurs in the tissues as small, round or oval yeastlike bodies, about 3 microns in diameter with a sharply defined capsule and a central chromatin mass These are found most frequently in the phagocytic reticulo-endothelial cells, although they may parasitize others of the blood and tissue cells For this reason the reticulo-endothelial organs, that is the spleen lymph nodes and bone marrow are commonly enlarged

Darling,^{1 2} who first described the disease, characterized it as having the prominent features of irregular fever emaciation and

splenomegaly. However, lymphadenopathy, ulceration of skin or mucous membranes, anemia and pulmonary or abdominal complaints all may be prominent features in an individual case. The disease always should be considered in the presence of splenomegaly, lymphadenopathy or anemia of obscure cause. Diagnosis depends on identifying the organism by examination of tissue, by culture or by inoculation of animals with material obtained for biopsy from lymph nodes, from the sternum by aspiration, or from other lesions (ulcers) or organs.

Although the patient represented in the following report of a case was an infant, the pertinent facts and findings were substantially all available and they are applicable to the adult.

CASE 19 *Histoplasmosis*—A white girl, seven months of age, was brought to the Clinic because of a persistent, septic type of fever, hepatosplenomegaly and marked anemia. In so far as was known, fever first had been noted when the child was six months of age and, two weeks later, an enlarged spleen was found. A diagnosis of hepatic disease had been made and treatment had consisted of administration of calomel, sulfa drugs and blood transfusions.

At the time of the child's admission to the Clinic approximately six weeks after the examination just mentioned, she appeared to be in fairly good general condition, in spite of the effects of progressive decline in weight and in general health during the previous month. Increased anorexia had required tube feeding. The baby's temperature, during the previous month, had ranged up to 105° F. Her previous history, as well as her family history, was not remarkable in any way. Laboratory findings on admission were as follows:

Urinalysis negative

Hemoglobin 12.6 gm per 100 c.c. of blood

Erythrocytes 3,640,000 per cu. mm. of blood

Leukocytes 1,900 per cu. mm. of blood

Differential leukocyte count, per cent: lymphocytes, 31.0
monocytes, 9.0
neutrophils, 60.0

Reticulocytes, per cent 5.2

Blood smear: hypochromic anemia, with increased regeneration and regenerative macrocytosis; neutrophils showed marked toxicity and there was considerable shift to the left.

Kline test for syphilis negative

Blood urea 26 mg per 100 c.c.

Serum bilirubin direct, negative

indirect, 0.8 mg per 100 c.c.

Albumin-globulin ratio 2.06/1.0

Agglutination tests for *Brucella*, *Eberthella typhosa*, *Salmonella paratyphi* and *Salmonella schottmulleri* negative

Liver function test (bromsulfalein) retention of dye, grade 1

Thick smear for plasmodia negative

Skin test for *Histoplasma capsulatum* negative

Roentgenologic examination of the head, long bones and thorax gave negative results.

Because of the marked leukopenia, anemia and septic course, bone marrow was aspirated from the tibia and, in this material, *Histoplasma capsulatum* was



Fig 117—Bone marrow elements from tibial puncture *a* monocyte containing five organisms of *Histoplasma capsulatum* within a large vacuole, *b* neutrophil showing degenerative changes with four or probably five organisms with its substance *c*, phagocytic reticulo-endothelial cell containing numerous organisms of *Histoplasma capsulatum*.



Fig 118—*a*, Colony of *Histoplasma capsulatum* cultured from the tibial marrow in case 19 ($\times 125$) This was cultured on blood agar plates Colonies became visible on the fourth day of incubation *b*, Portion of *a* showing the diagnostic tuberculate chlamydospores ($\times 900$)

found in the parasitized reticulo-endothelial cells, granulocytes and monocytes as well as in other bone marrow elements (fig 117, *a*, *b* and *c*) Following this finding, repeated tibial aspiration was done and the material was cultured Stools also were cultured and blood cultures were made While previous blood

cultures had been negative cultures from the tibial marrow on blood agar resulted in many colonies of *Histoplasma capsulatum* (Fig 118), while cultures of stool also yielded these same organisms. At no time on reviewing the blood smears was it possible to demonstrate *Histoplasma capsulatum*.

The child's course was progressively downward and she died a month after admission. At the time of necropsy all of her tissues were heavily infested with *Histoplasma capsulatum*.

Discussion of Case 19—While most reported cases of infection with *Histoplasma capsulatum* are concerned with infants, the disease occurs at all ages and, in any case in which the cause of splenomegaly, fever and abnormal blood findings is obscure, the diagnosis should be suspected. It was suspected in this case and skin tests were done before studies of bone marrow had been made. It is interesting that the result of the child's skin test was negative whereas the skin of the mother gave a positive test, although the mother gave no evidence of having the disease. Although careful examination of tibial marrow revealed the offending organisms, they might well have been mistaken for platelets or might have been overlooked altogether by one who was not familiar with the cytology of bone marrow. In cultures, however, organisms with the characteristic morphology were so prolific that the diagnosis would have been easily made by culture alone.

Infectious Mononucleosis.—Infectious mononucleosis is primarily a disease of children and young adults. It may be endemic on college campuses, in army camps and wherever young people gather. It is characterized clinically by lymphadenopathy, usually splenomegaly, malaise, general aching, a febrile course and, often, lesions in the mouth and throat. The disease may be extremely mild, or the degree of prostration and fever it causes may be alarming or occasionally, the severe abdominal condition secondary to adenitis may be mistaken for an acute surgical emergency. Not uncommonly there is a protracted period of fatigue and exhaustion after the disease has run its self limited course. The etiology of the disease is unknown.

Laboratory findings may be mistaken for those of leukemia, since there is variable leukocytosis, with absolute lymphocytosis, evidenced by the presence of abnormal, so-called leukocytoid lymphocytes. Recognition of these leukocytoid lymphocytes is important and the three types have been described by Downey and McKinlay.

In infectious mononucleosis, antibodies which cause agglutination of sheep erythrocytes usually are present, the agglutination is called an "heterophile antibody reaction." It is positive in about 80 per cent of cases of infectious mononucleosis but it also may be positive in the presence of serum sickness. It is negative in the leukemias and the lymphoblastomas.

CASE 20 Infectious Mononucleosis—A white girl, seventeen years of age, was admitted to the hospital with a sore throat and cervical adenitis. The throat had been sore for two days, then moderate chilliness, malaise and fever had come on and these manifestations had been followed by swelling of the cervical chain of lymph nodes.

On physical examination the following were found: congestion of the pharynx, follicular tonsillitis and, on the right side, some peritonsillar cellulitis. The cervical nodes were large, firm and very tender. The heart and lungs were negative, except for the presence of sinus arrhythmia. Examination of the abdomen gave negative results except that the spleen was found to extend for a distance equal to the breadth of one or two fingers below the costal margin. The patient's temperature was 102° F, the pulse rate was 104 per minute. Laboratory findings were as follows:

Urinalysis negative

Hemoglobin 13.5 gm per 100 c c

Red blood cells 4,350,000 per cu mm of blood

White blood cells 12,200 per cu mm of blood

Differential leukocyte count, per cent lymphocytes, 59.5

monocytes, 5.0

neutrophils, 35.0

metamyelocytes, 0.5

Blood smears "Picture of infectious mononucleosis—check heterophile antibody reaction"

Throat cultures no hemolytic streptococci

Blood cultures negative in 48 hours

Sedimentation rate 23 mm per hour (Westergren)

Heterophile antibody reaction positive, 2 plus, in dilution of 1:1,792 (18 hours)

Sulfadiazine was administered for five days and the tonsillitis and peritonsillar abscess subsided. In another five days, the girl was dismissed, at which time the cervical lymph nodes had receded remarkably and the spleen was no longer palpable.

Discussion of Case 20—The symptoms resembling those of influenza, which this young woman presented, together with the rapidly developing adenitis and splenomegaly, favor a diagnosis of infectious mononucleosis, particularly since the course was so short. However, it must be remembered that a large percentage of patients with leukemia date the onset of their illness from "an attack of flu" from which, they say, they never adequately recovered. The normal value for hemoglobin and the normal red blood cell count are very much against a diagnosis of acute leukemia, although toxic changes in the neutrophils favor a diagnosis of infectious mononucleosis. The condition of the throat in this case was more severe than that which ordinarily accompanies infectious mononucleosis. This girl actually had follicular tonsillitis, a peritonsillar abscess and associated infectious mononucleosis. Recognition, by the experienced hematologist, of the leukocytoid lymphocytes, and the positivity of the heterophile antibody reaction in high dilution, make the diagnosis relatively certain. The short course of the disease and

the return to normal health are final evidence of the presence of infectious mononucleosis. In an occasional case, persistent fatigue and exhaustion, as well as a few persistently swollen lymph nodes, are sources of worry to the physician but in due time these disappear

RETICULO-ENDOTHELIOSIS

Splenomegaly plays a prominent part in several diseases of the reticulo-endothelial system. Classification of these diseases is not entirely satisfactory. For clinical purposes they may be spoken of as (1) leukemic reticulo-endotheliosis, of which there are also sub-leukemic and aleukemic forms, (2) lipid diseases, in which the histiocytes from the reticulum cells store lipoids, as in Gaucher's and Niemann-Pick's disease and in the Hand-Schüller-Christian syndrome, (3) infectious hyperplasia of the reticulum.

Leukemic and Aleukemic Reticulo-endotheliosis—Leukemic reticulo-endotheliosis undoubtedly is a type of monocytic leukemia ("Schilling's monocytic leukemia") in which the reticulum cell is the progenitor of the leukemic monocytoïd leukocyte. The condition is a form of leukemia and the prognosis essentially is the same as it is in the other forms of leukemia. Leukemic reticulo-endotheliosis however, often presents a difficult diagnostic problem. The difficulty may arise because of the inability of the examiner to recognize the leukemic leukocyte or because the process is still largely confined to the bone marrow and spleen and, consequently, an obviously leukemic picture is not obtainable from the peripheral blood. The cell itself is primitive in appearance and often is larger than the other leukocytes in the blood smear. The nucleus is often eccentrically placed and frequently is ovoid and indented, however it may be rounded. The characteristic nuclear pattern is important to recognize. The chromatin is rather pale, very fine in structure and sharply delineated from the parachromatin. The nuclear membrane is clear-cut, smooth and stands out sharply. One or two nucleoli may be present. The cytoplasm is grayish blue or it may be so extremely pale that it is difficult to see at first glance. Commonly it is extremely ragged in the periphery and fades off, without having an obvious cellular membrane. The amount of cytoplasm may be proportionately greater than in the ordinary lymphocyte or monocyte. In cases in which the blood is typically leukemic, these cells are seen in abundance. In the subleukemic form however it may be necessary to search a long time even under the low power objective, in order to find these leukemic cells whereas in the aleukemic state, they will be found in relatively large numbers in preparations of sternal bone marrow.

The patient who has leukemic reticulo-endotheliosis usually presents himself with a complaint of weakness, perhaps of fever, of anemia and malaise. Commonly there are hemorrhagic manifestations, due to reduction in the number of platelets. The spleen is moderately or greatly enlarged. Unless patients present a frankly leukemic picture, usually leukopenia and relative lymphocytosis are definite. Anemia usually is present and, in more advanced cases, the hemorrhagic phenomenon, with prolonged bleeding time, no clot retraction, positive tourniquet test and low platelet count are present. The liver may be enlarged as a manifestation of this disease, although liver function tests usually give results which correspond with those obtained when the liver is normal. Commonly there is a history of some preceding chronic infectious process. The splenomegaly usually is of rather short duration as compared to the congestive splenomegaly of Banti's syndrome. In many cases encountered at the Clinic there has been a macrocytic anemia which has not responded to any treatment.

CASE 21 Leukemic Reticulo-endotheliosis—A white housewife, thirty-nine years of age, mother of three children, was admitted to the Clinic December 3, 1943, complaining of abdominal pain. Three months previously she had had what she thought was a cold. This had lasted longer than usual and the afternoon temperature had been 100° F. The woman had been given sulfonamides and a fine rash, with some pruritis, had developed. There had been a dull pain in the abdomen, not well localized, which occasionally had been stabbing in type. There had been recurring night sweats and the patient had noticed slightly enlarged cervical lymph nodes. Physical examination in November had disclosed splenomegaly and blood counts had suggested leukemia. The patient came to the Clinic for further opinion.

On physical examination, the woman was found to be well developed and well nourished but she complained of vague malaise and distress. She was notably depressed. Over the extremities were scattered petechiae and the tourniquet test was positive. The cervical lymph nodes were palpable and soft but otherwise were not remarkable. The spleen was easily palpable and slightly tender to pressure. Laboratory work revealed the following:

Urinalysis negative

Hemoglobin 12.7 gm per 100 c.c. of blood

Erythrocytes 3,660,000 per cu mm of blood

Leukocytes 17,200 per cu mm of blood

Differential leukocyte count, per cent lymphocytes, 31.0

neutrophils, 12.5

eosinophils, 1.0

reticulo-endothelial cells (leukemic),

55.5

Blood smear leukemic reticulo-endotheliosis

Discussion of Case 21—This case is rather a clear-cut one of leukemic reticulo-endotheliosis with a diagnostic blood picture. The history of a type of onset resembling that of influenza, together with

fever, petechiae and malaise, is typical. The important diagnostic point is to recognize the characteristic leukemic reticulo-endothelial cell.

CASE 22. Aleukemic Reticulo-endotheliosis—A white woman fifty-seven years of age came to the Clinic complaining of vaginal burning and vulvar pruritus which had been present for several years. In the lower part of the abdomen she also had some aching distress which had been present for many years. Fairly severe combined deafness made a satisfactory history rather difficult to obtain. However, it appeared that she had experienced some aching in the lower part of the back when she did heavy work and for this she blamed a "tumor of the spleen" which a physician had found about a year before. In the previous month she had had some night sweats. Also she complained of dyspnea on exertion and of muscular cramps coming on in the night. Possibly she had lost some weight. The patient was divorced but five of her children were living and well two sons had died. She had undergone laparotomy appendectomy removal of an ovarian cyst and removal of a "uterine tumor."

On physical examination the woman was found to be rather well developed. She weighed 120 pounds (57.2 kg). Blood pressures and temperature were normal. There was a soft systolic bruit at the apex of the heart. The spleen was enlarged 2 cm. below the level of the umbilicus and extended just over the midline to the right. The liver extended below the costal margin for a distance equivalent to two or three fingers breadths. Pelvic examination disclosed that the uterus was atrophic but the adnexa were negative to examination. Senile vaginitis was responsible for some bleeding on examination and was felt to be responsible for some spotting with blood which the patient had noticed in the past year. Menopause had occurred more than five years before. Laboratory findings were as follows:

Urinalysis negative

Hemoglobin 10.5 mg. per 100 c.c. of blood

Erythrocytes 4 080 000 per cu. mm. of blood

Leukocytes 1,300 per cu. mm. of blood

Differential leukocyte count, per cent lymphocytes, 50.0

monocytes 5.0

neutrophils 43.0

eosinophils 2.0

Blood smear anisocytosis with some polychromasia leukopenia with some shift to the left and toxic changes

Liver function test (bromsulfalein) retention of dye none

Serum bilirubin indirect 0.9 mg. per 100 c.c.

Sedimentation rate 33 mm. per hour (Westergren)

Kline test for syphilis negative

Sternal aspiration 75 per cent of cells with reticulo-endothelial characteristics differentiating into a lymphocytic type of cell

Roentgenologic examination of the thorax gave negative results

Discussion of Case 22—This case represents an aleukemic type of reticulo-endotheliosis. It was confused with Banti's syndrome until sternal aspiration disclosed its true leukemic nature. The patient's complaints were not at all clear-cut and physical examination revealed, essentially, nothing more than splenomegaly. There were hy-

pochromic anemia, leukopenia and neutropenia, with no immaturity being found on the blood smear. The patient might well have been subjected to splenectomy on the basis of the foregoing evidence, which suggested the presence of congestive splenomegaly. Careful search of the slide might have revealed characteristic leukemic reticulo-endothelial cells but sternal aspiration clearly established the diagnosis. The woman improved (hematologically) under cautious treatment with roentgen rays.

Gaucher's Disease.—This disease is a metabolic disturbance and the particular material involved is the cerebroside kersin. There is some question as to whether the disturbance is in the formation, transportation or storage of this material. The reticulum cells become swollen and engorged with deposits of kersin and this is the characteristic finding. These cells are most commonly present in the spleen, bone marrow, liver and, occasionally, lymph nodes and other organs. The cell has a characteristic reticular nucleus, usually with nucleoli, a fine arrangement of the chromatin network and a sharp nuclear membrane. The nucleus is often eccentrically placed and is relatively small compared to the large amount of cytoplasm. The cytoplasm is characteristic in that it contains fine fibrils, between which is deposited the kersin. This material does not stain with the usual stains or with fat stains.

Clinically, the disease is of more common occurrence among females than males. It tends to affect members of the same families and Jews. The disease usually is discovered in early childhood and its course usually is exceedingly chronic. The average length of life is about twenty years. There are patients, however, who live into late middle age. In some cases, however, the course is rapid and death occurs early in life. Death is due, not to the disease itself but to complications of anemia, hemorrhage or intercurrent infection.

An enlarged spleen usually is the first evidence of the disease. Later the liver usually enlarges and bone pain may be a prominent feature because of invasion of the marrow by local tumors. The patients often present distinct splenomegaly and, when they are seen late in the course of the disease, cachexia, anemia and purpura are prominent features. Exposed parts of the skin usually have a peculiar yellowish brown pigmentation and there commonly are pingueculae in the conjunctiva. Roentgenologic examination of the bones, particularly of the femur, may disclose characteristic changes. Splenic puncture will yield the characteristic cells. Sternal aspiration may yield the cells and, if it does yield them, the diagnosis is established. Due to invasion of the bone marrow, there may be myeloid metaplasia of the spleen, while the peripheral blood may contain normoblasts and may give evidence of myeloid immaturity.

(leukemoid reaction) Leukopenia may be present while thrombocytopenia is of common occurrence and accounts for the hemorrhagic tendency

CASE 23 Gaucher's Disease—A white housewife a Jewess came to the Clinic in November 1943 complaining of an enlarged spleen. As a girl, in Germany she always had appeared to be sickly but really had been relatively well. Her spleen however had been found to be enlarged when she was about twelve years of age. She gave no history of jaundice abdominal crises gastrointestinal hemorrhages or other complications. She had been married twenty years. She had gone through one normal pregnancy and had been delivered of a living child. Although her general health had been excellent, she had demonstrated some tendency to bruise in the years recently past and in the year just past, she had tired easily and did not feel "up to par." She believed that the spleen had enlarged more in the year just past than in previous years and that it filled much of the left half of the abdomen.

On physical examination the patient was found to be thin. She weighed 112 pounds (50.8 kg) and appeared ill. There was a sallow, yellowish brown discoloration of the exposed portions of her skin. Bilateral pingueculae were present but the sclerae were free of icterus. The shins were discolored from previous purpuric spots and the tourniquet test gave a strongly positive result. The spleen occupied the left side of the abdomen and extended downward to the pelvic brim and to the right of midline while the liver extended below the costal margin to a distance equivalent to three fingerbreadths. The remainder of the physical examination did not disclose anything remarkable. The family history did not contribute anything of value. Laboratory findings were as follows:

Urinalysis negative

Hemoglobin 8.5 gm per 100 c.c. of blood

Erythrocytes 3 190 000 per cu. mm of blood

Leukocytes 1500 per cu. mm of blood

Differential leukocyte count per cent

lymphocytes	24.0
monocytes	8.0
neutrophils	62.0
eosinophils	2.0
basophils	2.0
myelocytes	1.0
promyelocytes	1.0

Reticulocytes per cent 2.7

Platelets 57 000 per cu. mm of blood

Bleeding time 6 minutes

Fragility of red blood cells normal

Coagulation time 9½ minutes

Clot retraction slight in 24 hours

Prothrombin time (Quick) 18 seconds

Liver function test (bromsulfalein) retention of dye none

Sedimentation rate 24 mm. per hour (Westergren)

Serum calcium 10.4 mg per 100 c.c.

Serum phosphorus 3.9 mg per 100 c.c.

Serum phosphatase 67 units (Bodansky)

Blood smear tendency to microcytosis moderate thrombocytopenia with occasional myeloid immaturity

Sternal aspiration some shift to the left in myeloid and erythroid elements a number of Gaucher's cells found

Roentgenologic examination of the thorax and skull gave negative results. Reports of other roentgenologic examinations, however, read as follows: 'Changes in left innominate bone consistent with Gaucher's disease. Some expansion in distal end of left femur and mottled areas of rarefaction consistent with Gaucher's disease.'

Discussion of Case 23—The finding of Gaucher cells on sternal aspiration definitely establishes the diagnosis in this case. However, even if the typical cells had not been found, the extremely long illness, the pigmentation of the skin, the presence of pingueculae, the roentgenologic changes in the bones and the myeloid immaturity in the blood smear still would have been suggestive of Gaucher's disease. The fact that the values for all bone marrow elements in the peripheral blood were low suggests that the marrow was being replaced by some other tissue. The tremendous splenomegaly, the long course of the disease and the myeloid immaturity suggest that myeloid metaplasia of the spleen was present.

LYMPHOBLASTOMA

General Description.—This term is used loosely to designate the group of diseases of the lymph nodes which includes Hodgkin's disease, lymphosarcoma, giant follicle hyperplasia, and so forth. Since all of these conditions present essentially the same clinical problem, it seems reasonable to discuss them together. It should be remembered that these diseases may simulate practically all other conditions, to confuse the diagnosis. As is true of syphilis, so of this group of diseases, they can be great impersonators of other diseases.

The conditions under consideration are characterized by hyperplasia of lymphoid tissue and progressive changes that ultimately lead to death of the patient. These changes in the lymph nodes are susceptible to irradiation therapy and this characteristic often is useful in helping to establish a diagnosis. An interesting feature that I have observed in the histories of many of these patients is that adenopathy may be recurrent and remissions may be spontaneous. Finally the adenopathy persists.

Since this nodular enlargement, or diffuse proliferation of lymphatic tissue may occur in any portion of the body, problems involving any system may arise. Neurologic lesions, thoracic pathologic changes and gastro-intestinal symptoms all may be part of these diseases. The patient complains of lymphadenopathy in most instances. Peripheral adenopathy, however, may be minimal and the patient may complain of trouble referable to some system of the body. Most common of these complaints are those referable to the thorax, then the conditions of which the patients complain are attributable to involvement of mediastinal nodes or to diffuse involvement of the parenchyma of the lung. Vague abdominal distress,

due to retroperitoneal lymphadenopathy is of common occurrence, while loss of weight, fever of low grade, night sweats and toxic pruritus, often accompanied by toxic or exfoliative dermatitis, are features of common occurrence. Pain, particularly pain of a root type and extending into the lower extremities, often is distressing and probably is due to involved nodes pressing on the nerve roots. However, the pain may result from infiltration of the nerve roots.

Involvement of the bone marrow often will give a leukemoid reaction attended by myeloid immaturity which may simulate a leukemic picture, or, due to replacement of the marrow by lymphoblastomatous cells, values for red and white blood cells, platelets and hemoglobin may be very low. In some cases, large pathologic lymphocytes can be seen in the blood smear and this should arouse the physician's suspicions that a lymphoblastoma is present. In many cases, particularly cases of Hodgkin's disease, the neutrophils give considerable evidence of toxicity and monocytosis and eosinophilia are present. As with any debilitating disease, hypochromasia may be outstanding.

Splenomegaly is a frequent finding in cases of lymphoblastoma. In an occasional case, it may be the outstanding feature and peripheral adenopathy may be lacking. In questionable cases, roentgen therapy applied to the spleen usually is followed by definite improvement in the patient's condition and by shrinking of the spleen.

Diagnosis is established definitely by microscopic examination of tissue taken for biopsy.

CASE 24 Lymphoblastoma—A white housewife, forty-two years of age, came to the Clinic complaining of cough, weakness and loss of weight. While her symptoms had been much worse in the seven months before her admission, she felt that she never had been really well since her last pregnancy seven years before. In the course of that pregnancy she had lost weight, she had sustained a difficult delivery and then had continued to be chronically ill and debilitated. Four years before her admission dermatitis had developed and, two years later a diagnosis of pellagra had been made. This had responded well to specific therapy but the patient as a whole had not responded as had been expected. She had lost 30 pounds (about 14 kg.) during this period and she still was weak, nervous and easily exhausted. Seven months before her admission a persistent cough had developed, had become productive, and afternoon fever with the temperature rising to 101° F., and night sweats had appeared. Nausea and morning vomiting had been troublesome since the cough had been severe. The patient had had anemia for several years and it had been treated sporadically with liver and iron. A week before her admission, she had been examined at another clinic where an enlarged spleen had been found.

Later information was secured from the woman's home physician that radium had been applied for a large squamous cell epithelioma of the uterine cervix four years before her admission at the Clinic.

Physical examination revealed that the woman was thin and pale. Her blood pressures were 104 mm. of mercury systolic and 64 diastolic. The pulse rate was 86 a minute and the temperature 99° F. There were a few fine moist

râles in both pulmonary fields The liver was easily palpable and it had a sharp border The spleen extended a full hand's breadth below the costal margin The vagina was atretic from the effects of radiation but no evidence of recurrence of the cervical malignant growth could be felt.

The tissue of the left breast was thickened in one indistinctly circumscribed place and manipulation of this portion caused some dimpling of the skin There was a slightly enlarged lymph node in the left axilla but no other adenopathy Laboratory findings were as follows

Urinalysis specific gravity, 1.016

albumin, grade 2

pus, grade 2

Hemoglobin 10.5 gm per 100 c.c. of blood

Erythrocytes 4,550,000 per cu. mm. of blood

Leukocytes 6,600 per cu. mm. of blood

Differential leukocyte count, per cent lymphocytes, 50.0

monocytes, 3.0

neutrophils, 46.5

eosinophils, 0.5

Platelets 81,000 per cu. mm. of blood

Bleeding time $3\frac{1}{2}$ minutes

Blood smear hypochromasia, increased regeneration with mild macrocytosis, some toxic changes with a rare myelocyte and normoblast

Kline test for syphilis negative

Blood urea 24 mg. per 100 c.c.

Serum bilirubin indirect, 1.0 mg. per 100 c.c.

Sedimentation rate 10 mm. per hour

Sputum negative

Stools negative

Liver function test (bromsulfalein) retention of dye, none

Agglutination test for Brucellosis negative

The report on anteroposterior roentgenologic examination of the thorax was as follows "Localized infiltration left cardiophrenic angle. Some suggestion of bronchiectatic dilatation. Infiltration first and second interspace anteriorly, right, suggestive of pulmonary tuberculosis.

A lateral roentgenogram of the thorax resulted in the following report "Localized area of infiltration in left base is posterior and fairly well circumscribed, about 4 or 5 cm. in diameter. Rule out primary carcinoma."

Bronchoscopic examination gave a negative result.

In view of the indeterminate nature of this entire case, it was felt that the lesion of the left breast which, to the palpating hand seemed to have characteristics of malignancy, should be subjected to biopsy. In carrying out this recommendation, the diffuse nature of the lesion was considered, consequently, simple mastectomy was performed and an axillary lymph node was excised. Microscopic examination of the removed tissue resulted in a diagnosis, with reference to the breast tissue, of lymphosarcoma and, with reference to the axillary lymph node, that it had undergone inflammatory change.

Roentgen therapy was followed by considerable temporary improvement although developing leukopenia necessitated its discontinuance. Four months later, re-examination gave evidence of progression of the pulmonary infiltration and the patient's general condition was about the same as it had been before treatment. Further treatment was poorly tolerated and the patient died at home two months later.

fibrosis through the marrow cavity¹⁰ Unless it is possible to get a section of spleen for histologic study, diagnosis according to the foregoing criteria cannot be completely established For practical purposes, I feel that a case might best be considered an example of this syndrome if it presents the following features marked splenomegaly, known to have existed for a long time, hypoplastic bone marrow or roentgenologic evidence of fibrosis of the bone marrow, a leukopenic blood picture, including enough myeloid immaturity to raise the question of leukemia Supportive and symptomatic treatment would be a method of choice in handling such a case and irradiation and splenectomy, as has been said, would be avoided The following is probably a case of the syndrome in question

CASE 25 *Agnogenic Myeloid Metaplasia of the Spleen*—A white woman, fifty-eight years of age, first came to the Clinic in February, 1943, with a complaint of "blood disease" The patient had undergone surgical operation elsewhere twelve and eighteen years before and, on both occasions, had been told that she was anemic The only complaint she had made relative to her gastrointestinal tract was of vague dyspepsia Two years before she came to the Clinic, she had been examined because of weakness, fatigue, occasional nausea, vomiting and recurring diarrhea A serologic test for syphilis had given a positive result and antisyphilitic treatment had been administered The patient had been sensitive to arsenic on two occasions and it had not been used for treatment Her home physician had caused serologic reactions to be performed primarily because he had found a very large spleen at the time of his preliminary examination, when the woman was complaining of nausea and diarrhea She had been receiving injections of liver extract as well as of bismuth during the two years preceding her visit to the Clinic but her anemia had been persistent.

On physical examination, the edge of the liver was easily palpated, while the spleen extended 2 inches (5 cm) below the umbilicus and to the median line Physical examination did not disclose anything else remarkable Laboratory examinations revealed the following

Urinalysis negative

Hemoglobin 8.7 gm per 100 cc of blood

Erythrocytes 3,850,000 per cu mm of blood

Leukocytes 10,600 per cu mm of blood

Differential leukocyte count, per cent	lymphocytes, 20.0
	monocytes, 3.5
	neutrophils, 63.5
	eosinophils, 3.5
	basophils, 0.5
	metamyelocytes, 3.5
	myelocytes, 2.5
	promyelocytes, 2.0
	leukoblasts, 0.5
	stem cells, 0.5

Blood smear a great deal of polychromasia, poikilocytosis and other changes, scattered myeloid immaturity of all forms back to the stem cell, question of a leukemoid reaction or leukopenic, myelogenous leukemia

Serologic tests for syphilis Kline 2 plus
 Kahn 3 plus
 Hinton, positive
 Wassermann, very strongly positive

Serum bilirubin direct, none
 Indirect, 0.5 mg per 100 c.c.

Blood sugar 92 mg per 100 c.c.

Blood urea 22 mg per 100 c.c.

Liver function test (bromsulfalein) retention of dye, none

Serum protein 7.3 mg per 100 c.c.

Sedimentation rate 67 mm per hour (Westergren)

Stool negative

Examination of urine for lead negative

Analysis of gastric content no free hydrochloric acid

Spinal fluid findings normal

Roentgenograms of the thorax disclosed some cardiac enlargement but roentgenologic examination of the stomach, colon, skull and femur give negative results.

Sternal aspiration was performed and the counts hematocrit findings and differential counts were essentially the same as those of the peripheral blood. There were, however a few more basophilic normoblasts in the aspirated material than in the peripheral blood, suggesting that sternal marrow had been obtained. The woman continued to receive antisyphilitic treatment at home until September 1944. At that time the spleen was of essentially the same size as before while the blood findings all were identical with those of the previous year. Four months later following a period of rest from treatment, the patient's status was the same. She then was given penicillin starting with 2,500 units and gradually increasing to 10,000 units every three hours for ten days. With this treatment, which has caused the spleens in other cases of syphilis to decrease in size, hers remained unchanged and her blood picture showed the same findings as before which were suggestive of leukopenic, myelogenous leukemia.

In view of the long duration of the anemia and splenomegaly the myeloid immaturity the hypoplastic bone marrow and the lack of response of the splenomegaly to adequate antisyphilitic therapy a diagnosis of agnogenic myeloid metaplasia of the spleen was made.

Discussion of Case 25—The diagnosis in this case is presumptive and may be incorrect. It is made, however, largely by excluding other syndromes. After the exclusion, there are left the criteria of myeloid metaplasia of the spleen: long duration, large spleen, blood values suggesting poor function of bone marrow and immaturity compatible with myelogenous leukemia but without an elevated white blood count.

Cirrhosis of the liver with congestive splenomegaly, certainly is excluded by the normal serum proteins and normal results of the liver function test. Abdominal thrombophlebitis with secondary splenomegaly may be a possibility in view of the complaints referable to the gastro-intestinal tract and the elevated sedimentation rate. However the immaturity of leukocytes, in this case, to be a leukemoid reaction, should have been associated with a severe systemic re-

action, this patient was ambulatory and was well, as far as symptoms were concerned. While no other evidence of Gaucher's disease is present than splenomegaly, it is still not eliminated because the cells might not have been found in the material aspirated from the sternum. The possibility of leukopenic myelogenous leukemia being present is still existent and the material obtained on aspiration of bone marrow may have been primarily peripheral blood.

Repeated sternal aspiration might be helpful, while examination of an excised piece of bone marrow, to determine its structure, might establish another diagnosis. The elevated sedimentation rate is not adequately explained and gives rise to caution about a definite diagnosis. Syphilitic splenomegaly seems reasonably well excluded by the fact that, after two years of antisyphilitic therapy, followed by adequate treatment with penicillin, there was no change either in the size of the spleen or in the blood picture.

TUMORS OF THE SPLEEN

General Description.—Solitary tumors of the spleen occasionally occur and their diagnosis is practically impossible without exploration and demonstration of the tumor. The presumptive diagnosis is made after exclusion of other types of splenomegaly and is confirmed by exploration.

CASE 26 Splenic Lymphangiohemangioma—A white mother of three children, who was forty-two years of age, came to the Clinic in 1940, stating that two months before a tumor had been found in the left upper quadrant of the abdomen. She had been cognizant of some vague discomfort and heaviness in this region for six or seven years but never had noticed the tumor until a physician had found it on prenatal examination. An intravenous urogram had been made at home and left hydronephrosis had been reported. Since the finding of this tumor, the woman had had nausea and vomiting, anorexia, and had lost weight. Her past history had been essentially negative except that an ovarian cyst had been removed in 1928.

On physical examination, the patient was found to be well developed and well nourished, she weighed 122 pounds (55.3 kg). Her blood pressures were 150 mm of mercury systolic and 96 diastolic, the pulse rate was 90 per minute. The appearance of her breasts gave evidence of her pregnancy. The heart and lungs were negative to examination. The edge of the enlarged spleen descended to the level of the umbilicus. The surface of the spleen was irregular and it was difficult, from its contour, to be sure that it was spleen that was felt. The uterus was enlarged in accordance with a pregnancy of four months' duration. There was a small fibroid on the anterior surface of the uterus. Laboratory findings were as follows:

Urinalysis negative

Hemoglobin 10.2 gm per 100 c.c. of blood

Erythrocytes 4,510,000 per cu mm of blood

Leukocytes 4,700 per cu mm of blood

that a mass supposed to be an enlarged spleen actually is not spleen. The following cases illustrate this difficulty

CASE 27 *Leiomyosarcoma*—A white man, fifty-three years of age, came to the Clinic complaining of tiredness and weakness which had troubled him for two years. He had undergone appendectomy for acute appendicitis two years before his admission and he felt that he never had recovered his strength. The Wassermann reaction had been positive at the time of the operation and he had been given antisyphilitic treatment for eighteen months. Ten months before he came to the Clinic he had found that his abdomen was enlarged and that his clothes would no longer fit about the waist. Shortly before his visit to Rochester, splenic enlargement had been diagnosed. His past history, except that he had had pneumonia, was not remarkable.

On physical examination he was found to weigh 213 pounds (96.6 kg), although his weight four years before had been 250 pounds (113.4 kg). He was somewhat anemic. Blood pressures were 134 mm of mercury systolic and 90 diastolic. The pulse rate was 110 per minute. Examination of the thorax did not disclose anything remarkable. A large firm mass in the left upper quadrant of the abdomen extended into the right upper quadrant and the left lower quadrant. This was not tender to pressure, seemed to have a notch and was thought to be an enlarged spleen. Laboratory findings were as follows:

Urinalysis negative

Hemoglobin 10.5 gm per 100 cc of blood

Erythrocytes 4,400,000 per cu mm of blood

Leukocytes 8,900 per cu mm of blood

Platelets 99,000 per cu mm of blood

Bleeding time 3 min, 45 sec

Differential leukocyte count, per cent: lymphocytes, 16.0
monocytes, 6.0
neutrophils, 77.5
eosinophils, 0.5

Blood smear moderate hypochromasia, otherwise nothing diagnostic found

Sternal aspiration nothing diagnostic

Liver function (bromsulfalein) retention of dye, none

Sedimentation rate 90 mm per hour

Serologic test for syphilis: Kline, 2 plus

Kahn, 1 plus

Hinton, negative

Wassermann, very strongly positive

Roentgenologic examinations disclosed the following: A large, soft-tissue tumor filled the entire left portion of the abdomen and was thought to be spleen. Rheumatoid spondylitis involved both sacro-iliac joints and evidence was found of hypertrophic changes of the lumbar portion of the spinal column. The left ventricle was prominent and there was torsion of the arch of the aorta.

An excretory urogram revealed that the right kidney was urographically negative, while the left was in an indeterminate condition. The media in the left lower part of the ureter became normally concentrated in five minutes, which suggested that hydronephrosis did not exist and that the mass was not primarily renal.

Cystoscopy was performed in an attempt to make a left retrograde pyelogram but, due to irritability of the patient, this was not accomplished. It was advised that a further attempt be made with the patient under anesthesia but he refused.

It was felt that the splenomegaly was probably on a syphilitic basis and further antisyphilitic treatment and observation were advised. The patient, however, was further examined elsewhere and gastro-intestinal studies disclosed that the stomach was displaced upward, the colon downward and the small bowel to the right. The examiners made a diagnosis of pancreatic cyst and effected marsupialization of the cyst. Because of continued drainage the man returned to the Clinic two years later and, on exploration, diagnosis was made of *leiomyosarcoma arising from retroperitoneal tissue*

Discussion of Case 27—Here again a tumor in the left upper quadrant of the abdomen due to its irregular outline, seemed to present a notch to the examining hand. Tumors of the kind encountered in this case however, usually do not move with respiration. It often is possible, if the patient is relaxed, to pass the hand up over the tumor in a way not possible with the spleen which extends up under the costal margin. Because antisyphilitic treatment had been given for eighteen months without diminishing the size of the spleen, every possible diagnostic measure was taken to determine the nature of the mass. Most of the patients with supposedly syphilitic spleens whom I have happened to see because of hemolytic findings have proved to have spleens of another type. Roentgenologic gastro-intestinal findings indicated that the mass in this case was not spleen but exploration was necessary to prove its true nature.

Case 28 Hypernephroma—A white woman, forty-one years of age mother of four children came to the Clinic because of abdominal cramps which had been recurring during the past six months. She had not felt well for the previous three years. Constipation had been developing during the previous few months. The cramps started in the left upper quadrant of the abdomen and spread over the lower part of the abdomen. The constipation had been sufficient to require enemas or cathartics, and the stools therefore, had been watery. The pains did not seem to have any relationship to meals but were relieved after the bowels had moved.

The woman's past history had not been remarkable and she had gained more than 10 pounds (4.5 kg) in the last year. On physical examination, she was found to be short and stocky. Her blood pressures were 140 mm of mercury systolic and 80 diastolic; pulse and temperature were normal. Examination of the heart and lungs did not disclose anything of note. In the left upper quadrant of the abdomen there was a large, firm mass that, although it was somewhat rounded, seemed to present a definite border. Its surface was somewhat irregular and it extended from deep in the flank anteriorly and downward, to the umbilicus. This was thought to be spleen. It was believed, however, that an excretory urogram should be made to rule out a renal pathological condition. Laboratory findings were as follows:

Urinalysis specific gravity 1.017
 reaction, acid
 albumin, grade 2
 pus grade 1
 casts a few hyaline

Specimen of vesical urine no growth of organisms

Hemoglobin 9.6 gm per 100 c.c. of blood

Erythrocytes 4,790,000 per cu mm of blood

Leukocytes 8,100 per cu mm of blood

Blood smear aside from some hypochromasia, nothing diagnostic found

Kline test for syphilis negative

Sedimentation rate 45 mm per hour

Stools no parasites, no ova

The roentgenogram of the thorax was negative. Roentgenologic examination of the abdomen gave evidence of calcified mass, measuring 12 by 9.5 cm., in the left upper quadrant of the abdomen. Lateral views showed this mass to extend from the posterior aspect of the abdomen to the anterior wall in an irregular, curved fashion, so that the contour was not unlike that of the spleen.

An excretory urogram disclosed the right kidney to be normal. In the left kidney, concentration of the media was normal but the pelvis was incompletely visualized and the calices were indeterminate. The upper and lower thirds of the left ureter were normal. The original calcified mass was in relation to the upper pole of the left kidney. A large upper calix was visible through the mass and, although this calix was definitely elongated, it did not present the typical deformity usually associated with a cyst. Cystoscopic examination gave negative results.

Because of the indeterminate nature of this mass, and the possibility of it being a calcified renal tumor, the kidney was exposed through a postero-lumbar incision. A large hypernephroma of the upper pole was removed with some difficulty. The pathologist reported "In the upper pole of the kidney is a semi-encapsulated, grade 3 adenocarcinoma, 12 cm. in diameter (hypernephroma type) undergoing extensive calcification. The tumor perforates the capsule but does not invade the renal vein. About 20 per cent destruction of kidney substance."

Discussion of Case 28—This case illustrates the wisdom of making an excretory urogram if splenomegaly is questionable even though the diagnosis of renal tumor cannot be definitely established. A left renal neoplasm commonly presents a tumor which is mistaken for spleen. In this case, the large amount of calcification was suggestive of a renal neoplasm rather than of a splenic tumor. The suggestive changes in the upper calices, represented in the excretory urogram, also were important. The anemia was of the hypochromic type and this type of anemia is commonly an accompaniment of any type of neoplastic disease. The elevated sedimentation rate also was in favor of a neoplasm, although the rate was not markedly elevated. In most cases of lymphoblastoma and blood dyscrasia, the sedimentation rate is not altered particularly, unless by the degree of anemia that is present.

The complaint referable to the bowel probably was based on a reflex or pressure phenomenon arising from the abdominal tumor. In the presence of hypernephromas that have undergone degeneration, the blood smear often will give evidence of myeloid immaturity and toxicity, that is, a leukemoid reaction, and it may be suggestive of a leukemic or lymphoblastomatous process.

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CLINICS ON OTHER SUBJECTS

ROENTGEN THERAPY FOR LEUKEMIA

WALTER C POPP AND CHARLES H WATKINS

ONE object of this paper is to set forth the classification of the leukemias used at the Clinic. The groups of leukemias, as well as their subdivisions, will be presented. The hematologic picture for the different types of leukemias and a plan for roentgen treatment as followed at the Clinic will be discussed. The description is far from complete in many details, but it is hoped that, even though the presentation is general, the ramifications in diagnosis and treatment of the leukemias can be appreciated readily.

Leukemia is a disease of the blood forming organs, of unknown etiology, characterized by (1) increased numbers of leukocytes in the circulating blood, (2) presence of immature cells in the circulating blood, (3) usually a secondary anemia and (4) varying degrees of lymphatic, splenic and hepatic enlargement. Fifty-five per cent of the patients are between the ages of thirty and fifty years. After the age of sixty years the incidence drops sharply although leukemia does occur later in life. Leukemia occurs relatively rarely before the age of six years, but it does occur in the first decade of life. The average age of patients with myelogenous leukemia is forty-one years; the average age of patients with lymphatic leukemia is forty-nine years. About 60 to 80 per cent of the patients are men.

DIAGNOSIS IN GENERAL

Leukemia may be divided into the two types, namely, myelogenous and lymphatic. These may be further divided into the acute, subacute and chronic forms. Although this classification of leukemia is generally accepted, further subdivisions are vitally important to satisfactory treatment and these will be outlined in some detail. The diagnosis of leukemia is based on a combination of clinical findings and accurate hematologic study. The hematologic study is most important since it influences the plan of roentgen treatment. The hematologic study should include determination of the level of hemoglobin and the number of erythrocytes and leukocytes differential smear, special examination of individual cells and determination of the number of platelets. The type of leukemia, the form of leukemia and the degree of its activity are all important in the plan of treatment.

METHODS OF ROENTGEN TREATMENT IN GENERAL

Many plans of roentgen treatment have been used in leukemia and we shall point out briefly some of the plans now commonly used

Treatment to the long bones, such as the femur, humerus and ribs, has been used to a considerable extent. We have not used this method because of the depressing effect on the hemopoietic system and its resultant dangers. The erythrocytes can be affected markedly and a too radical reduction in the leukocyte count may be produced.

Treatment to effect what is known as blood volume, which entails treatment to the mediastinum and abdomen, is used. We do not use this method because of the indefinite effect on adenopathy or splenomegaly. It has a tendency to produce roentgen sickness because large fields are used. Also the treatment may produce a dangerously erratic effect on the leukocyte count.

Treatment to the spinal column either through a single field to the vertebrae or through paravertebral fields is used less commonly. We do not use this method because of the indefinite effect on the areas of involvement. Even though the leukocyte count is reduced, symptomatic improvement does not manifest itself in reduction of enlargement of the lymph nodes to any marked degree.

Irradiation of the entire body which is known generally as the Heublein or Teschendorf method has been used to some extent. This method consists in exposing the entire body to radiation of low intensity over a prolonged period. The hypothesis on which this method was based was that malignant cells were more susceptible to radiation in the mitotic period than in other phases. A specially arranged room and a long target-skin distance are necessary to carry out this procedure. Its use has been limited and the results do not seem to warrant installation of special equipment.

We prefer the methods which will be described in this paper. We feel that the results with these methods are better because better clinical improvement can be obtained than with other methods. The reduction in adenopathy and splenomegaly is marked. The use of many fields permits the use of small areas of treatment and small doses of roentgen rays. The leukocyte count is less inclined to show radical changes and the cutaneous reaction to roentgen treatment is minimal or absent. Roentgen sickness is either absent or mild. The erythrocyte count is usually unaffected by treatment.

MYELOGENOUS LEUKEMIA

Myelogenous leukemia is divided into the acute, subacute and chronic forms and the leukopenic and aleukemic varieties.

Forms.—*Acute* Acute leukemia usually occurs in patients less than twenty five years of age. Usually it has a sudden onset, often with an acute infection, and is associated with high fever, prostration and anemia. The spleen may or may not be palpable. Hemorrhages into the skin and mucous membranes, viscera and fundus of the eye frequently occur and ulcerations in the mouth and throat may occur. The white blood cell count rises rapidly, although it usually does not reach the level attained in the chronic form of the disease.

The acute form must be distinguished from the various forms of thrombopenic purpura (purpura hemorrhagica) and aplastic anemia. Thrombopenic purpura has a tendency to exhibit remissions and exacerbations over a relatively long period and as a general rule, the clinical symptoms are not as severe as those of acute leukemia. In aplastic anemia the stained smear reveals a decreased regenerative activity of the myeloid leukocytes, rarely any immature forms, relative lymphocytosis and thrombocytopenia, and decreased number of reticulated erythrocytes. In acute myelogenous leukemia the predominating leukocyte is the myeloblast or stem cell, with other myeloid leukocytes in varying stages of development. If this blood picture is found in association with the clinical features described, a diagnosis of acute leukemia is warranted.

Subacute—Subacute myelogenous leukemia is usually less dramatic in onset than the acute form, although as the disease progresses it may resemble acute leukemia. Hemorrhages occur as a result of reduction in the number of platelets. Fever and anemia are usually present. The spleen is usually palpable. An examination of stained blood films shows the predominant cells to be leukoblasts and relatively few myeloblasts or stem cells. Many promyelocytes and occasional myelocytes are seen. It is important to establish the diagnosis of subacute myelogenous leukemia because, in most instances treatment is contraindicated. It is likely that many cases of subacute leukemia are really mild forms of the acute form and in these cases roentgen treatment should be avoided. In occasional instances, however, a rather high proportion of immature cells may be associated with an almost equal number of relatively mature leukocytes and a moderate reduction in the number of blood platelets.

Chronic—Chronic myelogenous leukemia is usually characterized by the slow insidious onset of anemia, gradual enlargement of the spleen and progressive increase in the number of myeloid leukocytes. Weakness and loss of weight are almost always present. Frequently the initial complaint is that of a tumor in the left upper

quadrant of the abdomen Enlargement of peripheral nodes may be present, but this is relatively uncommon in myelogenous leukemia Examination of stained smears shows a marked increase in the number of myeloid leukocytes The predominant cells are mature neutrophils, but metamyelocytes and myelocytes are rather numerous Cells of greater immaturity are present, but in comparison with the number found in the late phases in the development of myeloid leukocytes, myeloblasts, leukoblasts, and promyelocytes, they are not numerous

Varieties.—*Leukopenic* Leukopenic leukemia may occur in any of the previously described forms of myelogenous leukemia The clinical findings and the result of study of the individual cells are similar to those found in myelogenous leukemia, but the total leukocyte count proves to be at a normal level or below it The diagnosis depends on an analysis of stained blood smears When leukopenic myelogenous leukemia occurs in the acute or subacute form, roentgen treatment should not be given under any circumstances, because of the possibly disastrous effect on the total white blood cell count

Aleukemic—Aleukemic myelogenous leukemia is now believed to be a separate variety of the previously described forms of leukemia The diagnosis is made by examination of bone marrow The blood in the peripheral vessels usually does not contain cells which are characteristic of leukemia, but the marrow shows the characteristic changes

Treatment—*General* Since roentgen rays were first used for the treatment of leukemia in 1902, a number of methods have been advocated The rationale of roentgen treatment is not yet clear, and the literature on the subject contains many unanswered questions For example, it is known that remission of the disease may be produced by irradiation of the spleen, and yet leukemia is defined as a disease of the blood-forming organs Why do remissions occur when only the spleen is irradiated? If the rays act by destroying white blood cells, why do not these cells regenerate immediately after those in the blood and in the spleen have been destroyed? That the process of regeneration is a general one is well known If treatment is successful because of destruction of cells, why do patients with the aleukemic form of myelogenous leukemia improve clinically while the total white blood cell count may remain unchanged? Is there a ferment or is an unknown substance liberated in the blood which inhibits the production of leukocytes, or does a chemical change occur in the blood stream?

As has been said, the types of radiation therapy which have been used are irradiation of the spleen, long bones, mediastinum

and flat bones. More recently irradiation of the entire body, using penetrating rays at a long target skin distance, has been employed. In recent years radioactive phosphorus has been employed as a form of treatment, but this will not be discussed in this paper.

We employ the method of treating the spleen through multiple small fields, varying the dose according to the phase of leukemia. Our experience has led us to conclude that moderate voltage, in the range of 130 to 140 kilovolts, is more effective than any other voltage. The area corresponding to the spleen is divided into nine fields of approximately equal size. Usually four anterior fields, four corresponding posterior fields, and one lateral field are used. By using nine separate fields nine sessions of treatment can be given, if this is indicated, without repeating the exposure of any one field. Before treatment is started, the status of the patient's white blood cell count, erythrocyte count, hemoglobin and platelet count must be investigated carefully. In cases in which severe anemia is present, transfusion may be indicated, but if anemia is moderate, transfusion is not necessary, since a decrease in the total leukocyte count is not uncommonly associated with a corresponding rise in the erythrocyte count.

Treatment is instituted on one of the lower splenic fields, and on the next day a leukocyte count is made. Treatment always depends on the results of the daily leukocyte count. Often the first or second leukocyte count after the start of treatment shows an increase over the original count. The hypothesis that roentgen rays stimulate cells has been well nigh abandoned but for some reason this initial increase often occurs. Daily treatment is continued and the leukocyte count is made each day until it reaches a satisfactory level. This level varies considerably according to the type and form of leukemia. In chronic myelogenous leukemia the leukocyte count may diminish much more quickly under roentgen treatment than in subacute or aleukemic leukemia. When the count seems to decrease too rapidly, treatment should be discontinued for twenty four or forty eight hours, in order to evaluate the significance of this decrease. We believe that treatment should be carried out in a relatively short period so that the patient may carry on without treatment as long as possible. This plan has been found to yield better palliation than haphazard treatment at irregular intervals. Treatment is resumed when the total leukocyte count begins to show a definite and persistent increase and immature forms reappear.

It does not follow necessarily that the higher the count the greater the amount of treatment needed. Patients with relatively low counts of from 75 000 to 100 000 cells in each cubic millimeter of blood usually need more treatment to produce the desired effect.

than patients with cell counts of 200,000 to 300,000. The leukocyte count should not be allowed to fall below certain flexible limits depending on the original count. When, for example, the original count is 75,000 cells, treatment should not be carried beyond a point at which the count reaches 25,000. When the original count is 250,000 cells, treatment should not be carried past the point at which the count reaches 50,000 to 60,000 cells. The reason for this precaution is that the leukocyte count may continue to decrease for a month or more after treatment has been stopped. Should the treatment be carried beyond a reasonable level severe leukopenia may develop. If the patient had a high original count, which treatment has reduced to 50,000, the leukocyte count usually reaches a satisfactory level three weeks after treatment has been discontinued. When patients have mild leukocytosis, their general condition seems to be better than when they have a so-called normal leukocyte count or leukopenia.

When the course of treatment averages from seven to nine days, control of leukemia is easier and subsequent treatment, when this becomes necessary, is facilitated. The use of a large number of small fields permits a fairly large number of treatments with little or no dermal reaction, and causes little radiation sickness.

Acute Form—The treatment of acute myelogenous leukemia with roentgen rays is useless. The clinical course of the disease is so rapid that treatment has little if any effect on the erratic white blood cell count. In isolated instances treatment with roentgen rays may be of value for superficially located leukemic infiltration, but this is the exception rather than the rule. Blood transfusion and other supportive measures may be of limited but doubtful value.

Subacute Form—In spite of the rapid onset of subacute myelogenous leukemia, in isolated cases it may respond temporarily to small doses of roentgen rays. Treatment involves using nine fields, as we already have suggested, however, the dose per field should not exceed 75 to 80 r measured in air. This is a small dose, but in this type of leukemia larger doses are to be avoided. This dose is sufficient to produce the desired effect on the leukocyte count. Treatment is given every day until a satisfactory result is obtained. As a rule, treatment is interrupted when the leukocyte count has reached a level of approximately a third of the original count. When the original count was 150,000, the course of treatment should be interrupted when the count reaches approximately 50,000. Because of the radiosensitiveness of the cells in subacute myelogenous leukemia and the sometimes erratic response to treatment, the risk in excessive roentgen treatment is great because the destruction of an excessive number of leukocytes may be fatal.

Chronic Form—Chronic myelogenous leukemia is the least difficult form of leukemia to treat, and the results obtained usually are much more satisfactory than in other forms. The dose used in each of the nine fields is approximately 225 r (measured in air). Treatment is given daily as long as the leukocyte count does not diminish too rapidly. When the count reaches the desired level, treatment is interrupted and the patient allowed to go without treatment until a definite tendency for the count to increase is observed or until the patient's clinical symptoms recur. Here again the original count is important in determining the level to which the leukocyte count should be permitted to fall. When, for example, the original count before treatment was 300,000 the leukocyte count may safely be permitted to fall to a level of about 75,000. When the original count was 150,000, treatment should be suspended when the count has reached a level of 25,000 to 35,000. When the original count was 75,000, it can safely be reduced to 20,000 to 25,000. In this type of leukemia the count should not be allowed to fall below 20,000, unless the original count was not higher than 20,000. With an original count of about 20,000 cells treatment may be given until a level of about 10,000 is reached.

Leukopenic Variety—In the leukopenic type of myelogenous leukemia treatment involves the use of the nine fields but owing to the low total leukocyte count, it should be administered with caution. The daily dose should not exceed 75 r (measured in air) and small fields should be used. A careful watch of the leukocyte count is, of course, absolutely necessary. Often a course of treatment will produce little change in the leukocyte count, but it may induce gradual reduction in the size of the spleen and clinical improvement. Usually not more than five sessions of treatment are necessary and treatment is stopped whenever the leukocyte count shows any tendency to decrease.

Aleukemic Variety—Treatment of aleukemic myelogenous leukemia presents much the same problem as the treatment of leukopenic myelogenous leukemia. The leukocyte count may vary from 2,000 to 10,000. Fifty to 75 r is used with small fields and the same precautionary measures described for the leukopenic phase must also be observed. If the original count was 5,000 treatment should be stopped when it has reached a level of approximately 4,000. If the decrease with the initial treatment is sudden then twenty-four to forty-eight hours should elapse before further treatment is administered. The count will usually return to a safe level. If the original count was 10,000 treatment may be continued until the count has reached a level of 7,000. Patients with aleukemic leukemia may have remissions with almost normal health for as long as a year following adequate roentgen treatment.

LYMPHATIC LEUKEMIA

Lymphatic leukemia is divided into acute, subacute and chronic forms and chronic macrolymphocytic and mesolymphocytic varieties

Forms.—*Acute* Acute lymphatic leukemia is much more rare than acute myelogenous leukemia, at least in adults. Some investigators believe that because the stem cells of both myeloid and lymphoid tissues are similar and because the clinical, hematologic and pathologic aspects of the acute form are similar, there is but one type of acute leukemia and that the cells are neither lymphoid nor myeloid but undifferentiated

In acute lymphatic leukemia enlargement of the lymphatic structures may be slightly more general than in myelogenous leukemia and the spleen may be slightly enlarged

The more immature cells predominate in the blood picture. Lymphoblasts are numerous, and the blood smear has more uniformity than diversity of cell type

The clinical symptoms and signs of acute lymphatic leukemia resemble closely those of acute myelogenous leukemia

Subacute—The subacute form of lymphatic leukemia may be either a mild form of acute lymphatic leukemia or an acute exacerbation of unrecognized chronic lymphatic leukemia. The common cell in the blood smear is also the lymphoblast or stem cell. Some authors do not even recognize a subacute form

Clinically these patients will develop varying degrees of enlargement of the lymphoid tissues of the body

Chronic—The age incidence is higher than for the other forms and types of leukemia and it occurs more frequently in males than in females (31). The onset is usually unknown and is insidious in character. Usually the first symptom is painless swelling of the lymph nodes and the superficial nodes, naturally, are among the first ones observed. Varying degrees of enlargement are found usually in the cervical, supraclavicular, axillary and inguinal nodes. Roentgenograms of the thorax may or may not be useful in determining the enlargement of lymph nodes. The retroperitoneal lymph nodes can usually be palpated if they are enlarged and varying degrees of splenic and hepatic enlargement may be encountered. The nodes involved are usually discrete and not matted together as are inflammatory nodes. They have a firm fullness but are usually not as hard as the lymph nodes of Hodgkin's disease or metastatic malignant disease

Weakness, pallor, loss of weight and general malaise are among the symptoms most frequently found. Careful inquiry into the patient's history usually reveals that he has had malaise for several months but usually no specific date of onset is given

The leukocytes in the blood of patients with chronic lymphatic leukemia usually present a striking uniformity in contrast to the blood picture of chronic myelogenous leukemia. In the typical case, the leukocytes are usually mesolymphocytes and microlymphocytes and these constitute 75 to 95 per cent of the total leukocytes. The younger leukocytes frequently contain a more basophilic cytoplasm and a more delicate chromatin network in the nucleus and may contain nucleoli.

Chronic Macrolymphocytic and Mesolymphocytic—The clinical features of this variety of lymphatic leukemia are in no way different from the picture to be found in any other lymphatic leukemia. The diagnosis must be made by careful examination of the blood smears by a competent hematologist.

It was found that in certain cases of chronic lymphatic leukemia a much greater sensitivity to roentgen rays is exhibited than in the ordinary form of lymphatic leukemia. In reviewing the blood picture of these cases it was found that a large majority of the lymphocytes were of the macrolymphocytic and mesolymphocytic type rather than microlymphocytes and mesolymphocytes which usually predominate. Furthermore, the blood picture in these cases might even be confused with the blood picture found in acute lymphatic leukemia. However, a study of these immature cells reveals that they are not lymphoblasts nor are they the usual type of lymphocyte found in chronic lymphatic leukemia. These cells have a large nucleus and abundant cytoplasm. The nuclear chromatin is of the heavy black type usually seen in mature lymphocytes and distinction from the immature lymphocytes may readily be made by this nuclear pattern. About 5 per cent of the cases of chronic lymphatic leukemia are of this type.

Treatment.—Acute Form. Treatment for acute lymphatic leukemia is the same as for acute myelogenous leukemia. Some therapists have stated the opinion that in some acute cases light doses should be used in the hope that the acute form of the disease will turn into the chronic form. It is doubtful that roentgen treatment had anything to do with the change in the leukemia. We feel that treatment in a true acute leukemia is of no value.

Subacute Form—The treatment of subacute lymphatic leukemia is likewise of doubtful value. However, if treatment is to be given, it must be given carefully. As in the treatment of subacute myelogenous leukemia smaller doses of roentgen rays (not to exceed 75 to 100 r per field) must be used. The areas of involvement whether they be the cervical or supraclavicular areas, axillae, retroperitoneal lymph nodes or the mediastinal nodes, are treated with 75 to 100 r to each field per treatment. One treatment is given each day and

the blood count is estimated daily. The same general rules which governed treatment of subacute myelogenous leukemia are applicable here. If the count decreases too rapidly, treatment should be withheld for from twenty-four to forty-eight hours. Treatment is stopped when a satisfactory level of the blood count is reached. If the original count was 150,000, the treatment is terminated when the count reaches approximately 50,000. Naturally greater care must be employed in treatment of this form of leukemia than of the chronic form because of the sudden changes which may occur in the leukocyte count.

Chronic Form—In chronic lymphatic leukemia, treatment of the involved areas is given for a variable number of days and the number of treatments depends on the elevation of, and effect of the treatment on, the leukocyte count. The principles of treatment as described in chronic myelogenous leukemia are applicable in chronic lymphatic leukemia. Treatment is administered to the involved lymph nodes instead of the spleen. The leukocyte count will decrease in much the same manner. The dosage (225 r per field daily) is comparable to that used in chronic myelogenous leukemia, and careful observations of the blood count should be made.

Chronic Macrolymphocytic and Mesolymphocytic Forms—In the treatment of this variety caution must be exercised. The use of higher doses of roentgen rays causes extreme fluctuation in the leukocyte count. A reduction of as much as 50 per cent can take place in twenty-four hours with excessive treatment. Although this rapid change is dangerous in any leukemia, the real danger in this form of leukemia is not only in the rapid reduction of the leukocyte count but in the effect on the chemical constituents of the blood. With a radical reduction of the leukocyte count, the level of urea in the blood may rise markedly in a period of from twenty-four to forty-eight hours. In some instances the concentration of urea in the blood may double or even triple. There are two possible explanations of this. One is that the sudden increase in waste products due to disintegration of leukocytes is more than the renal system can eliminate properly. The other more likely explanation is that leukemic infiltration involves the kidneys, especially in the region of Bowman's capsule. For the last few years at the Clinic we have instituted treatment of the posterior part of the abdomen, directing roentgen rays to the renal areas. It is felt that the effect on the leukemic infiltration in the kidney is such that renal function, with respect to the elimination of waste products, is improved. In treatment of this variety of leukemia determination of the concentration of urea daily is as important as a daily leukocyte count.

Treatment consists of irradiation of the regions of involvement.

Not more than 100 to 125 r per field should be used and a moderate voltage technic should be employed. One treatment a day is given until the leukocyte count reaches the desired level. The level to which the count is lowered depends on the original count. The rules for determining the level are the same as those previously given in the treatment of the subacute forms of leukemia. Occasionally the leukocyte count may not be reduced when treatment is given. The leukocyte count must be watched more carefully, because it may decrease suddenly and continue to fall for several days even though treatment is discontinued.

If the concentration of urea in the blood should increase, treatment must be interrupted for several days until it returns to normal. Should the concentration fail to return to normal or continue to increase, hospitalization and intravenous administration of fluids are indicated.

MONOCYTIC LEUKEMIA

Considerable disagreement has arisen regarding the terminology of this type of leukemia because various hematologists are unable to agree on the origin of monocytes. If the current classification of leukemias is to stand, two types of monocytic leukemia must be recognized namely (1) the *Schilling type* in which the cells are derived from the reticulo-endothelial system and (2) the *Naegeli type*, in which the monocytes are regarded as developmental products of the myeloid series, or a variety of myelogenous leukemia.

Clinically, the disease presents symptoms which closely resemble those of myelogenous leukemia, except in the *Schilling type*, in which considerable lymphadenopathy may be found. The findings are also compatible with those found in myelogenous leukemia.

The blood picture reveals large numbers of cells which can be identified as monocytes as well as larger, but apparently related, forms. The nuclei of the larger forms are irregular in shape and composed of fine reticular chromatin. The nucleus is more lacy than the nucleus of a typical monocyte. The cytoplasm is grayish blue and may contain innumerable fine dustlike, reddish lilac granules.

The roentgen treatment is similar to the treatment for myelogenous leukemia.

SUBLEUKEMIC SPLENIC RETICULO-ENDOTHELIOSIS

Subleukemic splenic reticulo-endotheliosis is characterized by anemia, splenomegaly, fever, purpura, leukopenia and thrombocytopenia. Examination of smears of blood from peripheral vessels reveals a few monocytes with definite characteristics of the

reticular cell, and these are slightly immature. This type frequently has been confused with so-called splenic anemia of Banti's type. A detailed description of this condition and the criteria for differential diagnosis have been presented by Giffin and Watkins¹.

Treatment of subleukemic splenic reticulo-endotheliosis presents the same problem as treatment of aleukemic and leukopenic myelogenous leukemia. The same precautionary measures are necessary in observing the daily leukocyte count. Daily dosage should not exceed 75 r and small fields of treatment of the spleen are used. The total leukocyte count usually does not exceed 10,000 and it need not be reduced below a level of 4,000 to 5,000. Good clinical response and reduction in the size of the spleen can be obtained.

COMMENT

In general, in acute leukemia the disease is active and death may ensue in a few days to a few weeks. In chronic leukemia the patient may live for from two to four years. In exceptional cases the process may be controlled for much longer periods. In the subacute forms the life expectancy will usually fall between these two extremes.

We feel that roentgen treatment is as good a therapeutic measure in cases of leukemia as is known at the present time. Although the effect is entirely palliative, yet with properly supervised treatment a patient can be maintained in a useful capacity. Much disagreement is apparent between hematologists and radiologists as to whether or not roentgen therapy prolongs life. We do not pretend to make any definite statement on this point except to infer that in some instances life seems to be prolonged considerably. Even though this may not be wholly true, the fact that the general health of the individual patient is usually maintained at a better level with the use of roentgen treatment is sufficient to warrant its acceptance as a therapeutic measure in the treatment of leukemia. We believe the close co-operation of the hematologist and the radiologist is important in the successful care of leukemia.

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TREATMENT OF HEADACHE

BAIRD T. HORTON AND DOROTHY MACY, JR.

MEDICAL literature is replete with observations on the causes and treatment of headache. This symptom is a constant challenge to physicians. Patients who consult a physician for other symptoms frequently fail to mention the presence of headache because of their firm belief that it cannot be relieved. No statistical data from a single medical center will furnish a true index of the importance of this symptom complex. Headache also is important from the economic standpoint. In one large factory this symptom accounted for 24 per cent of more than 15 000 absences of employees.

THE CLINICAL HISTORY

In any case of headache, it is most important to obtain a detailed history. A carefully taken history will furnish more clues to the underlying cause of the pain than will all other diagnostic procedures combined. Although the physician may assume that general physical examination, laboratory tests and special examinations of the nervous system and of the eyes, ears, nose and throat may disclose some organic lesion which is causing the headache, the results of these examinations usually are negative. If these examinations have been made before a detailed history is obtained, the physician usually will have to retrace his steps and obtain a detailed history. If he fails to do this, the treatment that he prescribes is not likely to be successful. We are well aware that headache can be caused by many organic lesions, but in most cases of headache observed in general practice the pain is not of organic origin. In the final analysis, the success that is achieved in the treatment of this symptom is directly dependent on the care that is exercised in obtaining a detailed history.

The Pain—Onset, Duration and Character. In order to obtain information about the onset, duration and character of the headache, the physician should ask the patient the following questions: What were the circumstances under which the pain first developed? Was the onset gradual or sudden? Was it in any way associated with trauma or an infectious process? Is the pain mild or severe? Is it constant or intermittent? Is it lancinating, throbbing or pulsating? Is it of a burning, boring type? Does it end abruptly or does it subside gradually? Does it persist for seconds, minutes, hours or days? When does the pain occur, night or day, or both night

and day? If it occurs during the day, does it remain constant throughout the time that you are awake? If it is not constant, does it occur in the early morning, in the middle of the day, or in the afternoon or early evening? If it occurs at night, does it ever cause you to awaken from a sound sleep? If it does, do you jump out of bed because of the severity of the pain or do you remain in bed? Does your posture seem to influence or precipitate the pain? Is any residual soreness present after the pain disappears? If there is, how long does it persist? Is the pain aggravated by sneezing, coughing, or placing your head in a dependent position? Is it precipitated by chewing? If it is, does discontinuing chewing relieve the pain? Does the pain occur in paroxysms? If it does, are all of the paroxysms essentially alike? Do they tend to recur at stated intervals, such as day after day, or night after night, for long periods of time? Has the pain incapacitated you or have you been able to do your routine work?

Site and Extension of the Pain—One should inquire whether the pain involves the entire head or is sharply localized in one region. The patient also should be asked whether the pain extends in any direction. If it does, an effort should be made to determine whether the site of extension corresponds to the anatomic distribution of one of the cranial nerves. The patient also should be questioned about the presence of "trigger zones" or points of tenderness in the superficial or deep tissues.

Effect of Previous Treatment—If the patient has been treated previously for the headache, he should be asked whether the pain has been relieved by special medication or by intranasal operation, cauterization of the sphenopalatine ganglion or injection of alcohol into one or more of the branches of the trigeminal nerve.

Associated Manifestations—The history frequently will disclose the presence of associated manifestations which will aid in classifying the type of headache. The physician should try to ascertain whether the patient is allergic to any article of food. In addition, the patient should be asked the following questions: Is the pain associated with redness, swelling and watering of the eye, or with plugging of the nostril on the involved side? Is it associated with nausea, vomiting, scotomas or sensitiveness to light? Is the pain seasonal in its occurrence? Is it associated with changes in environmental temperature? Is the onset of the pain related to the taking of food or the use of alcoholic beverages? Is the pain related to the menstrual cycle?

Nervous Tension—After the physician has obtained a detailed description of the pain, he should try to determine whether any nervous tension is present. Nervous tension is one of the most im-

portant and least understood components of the headache syndrome. In this article, the term "nervous tension" is used to designate a state of physiologic hypertonicity that is induced by the higher nerve centers. Headache is not caused by nervous tension but by the hypotonicity which replaces the hypertonicity. Headache that follows a state of high nervous tension should not be confused with psychogenic headache. To some extent, a psychiatric appraisal of each patient is necessary. An experienced clinician instinctively makes such an appraisal while he watches the patient and listens to his story. In some instances, it may require hours for the patient to tell his story but the physician usually will be rewarded if he will listen carefully.

In most cases, headache is of the nervous tension or psychogenic type. The demand for incessant adaptation in a world that is both civilized and "atomized" at times exceeds the reactive possibilities of the autonomic nervous system. As a result, the two divisions of this system become incoordinated. This predisposes to bodily dysfunction, of which the patient is often unaware. If the element of nervous tension which is an integral part of migraine, could be eradicated, more would be accomplished than by the use of all other procedures combined.

Galens account of "The lady and the dancer" indicates that he realized the etiologic role of nervous tension in clinical problems. The following quotation has been taken from Days book, "Head aches their nature, causes and treatment,"¹⁰ which was published in 1882:

"The subject of headache is of manifest importance, because it claims so many sufferers and is surrounded by so many difficulties—the pathology is obscure, the diagnosis perplexing, the remedies uncertain. Headache is a disorder of the utmost frequency and yet there is none which more taxes the experience and scientific knowledge of the physician, or requires closer observation in elucidating its nature and removing its obscurity.

"The young child is expected to grapple with abstruse questions which a few years ago were only intended for the advanced scholar and those who made philosophy their peculiar study. The microscope, with its revelations, the electric telegraph, which brings us in immediate contact with the enterprise and movements of other countries, are both powerful factors in stimulating the brain of man to unusual activity—and the generally increased pace at which we live have all tended to excite and exhaust the brain.

"Before civilization had arrived at its present high state, the overwrought brain was confined to men of letters and laborious students in the solitary contemplation of human knowledge. Nervous

exhaustion was not the common disorder we now find it, and physicians were nearly silent on the causes which produced it. In what ever direction a man now turns his attention, he is sure to see competitors who are striving for the same prizes. In trade, in commerce, in literature, and in art, it is ever the same—no man has the field to himself. It is not surprising that the complex and delicate structure of the brain and nerve should fail, under the continued strain and this struggle for existence in the battle of life.”

Day's comments appear even more applicable at the present time than they were in 1882. The element of nervous tension is not always easy to determine and is the stumbling block for most physicians. If they fail to appreciate its importance, they are liable to miss the core of the problem. We cannot overemphasize this point. Too many physicians approach the problem of headache with one thought in mind, namely, that they can find an organic basis for the patient's symptoms.

OBSERVATION OF PATIENT DURING AN ATTACK

In most cases of headache, the physician does not see the patient at the time of the attack. This accounts for the failure of treatment in many cases. In making an accurate diagnosis of the type of headache and in evaluating the patient's statements and the severity of the pain, nothing can surpass observation of the patient during a painful episode.

The understanding of headache tends to become simplified when one realizes that the pain is of vascular origin in practically all cases of headache. One can approach the problem from a physiologic point of view. The headache often can be reproduced so exactly that the patient cannot distinguish an induced attack from a spontaneous attack. This is especially true of histaminic cephalgia (Horton's syndrome).

ANATOMIC AND PATHOLOGIC CONSIDERATIONS

In this paper the term "headache" will be used to designate pain or paresthesia of the head or a hallucination of either of these manifestations. Paresthesia of the head is due to the same causes which produce paresthesia elsewhere in the body. It is well known that sensitivity to pain varies in different cases and at different times in the same case. The threshold of pain is decreased by fatigue or injury.

Sources of the Pain—Pain in the head may originate in one of the following anatomic structures ^{8 10, 17 19-22, 30 31, 33 36 38 39}
^{41-44 46-49} (1) the tissues covering the cranium, (2) the cranial periosteum and endosteum and (3) certain intracranial structures

Tissues Covering the Cranium—Pain that arises in the tissues covering the cranium may be muscular, neurogenic or vascular in origin. Muscular pain is due to a local accumulation of metabolites which may be the result of overproduction or failure of removal. The painful sensations in the head are the ultimate result of sustained muscular contraction. Sustained muscular contraction results in the accumulation of metabolites which in turn act on, or stimulate sensory nerve endings.³⁰ Primarily neurogenic pain is exemplified by neuralgia and neuritis. These pathologic conditions will not be considered in this paper. Vascular headache is caused by distention of, or traction on the walls of the vessels or by inflammation and thrombosis of the vessels.

Cranial Periosteum and Endosteum—Pain that originates in the periosteum or endosteum is due to a disruptive force that is exerted between the bone and either of these tissues.

Intracranial Structures—Although involvement of intracranial structures may cause pain in the head, it is interesting to realize that the cranium, the brain itself, most of the dura, the pia, arachnoid, the choroid plexus and the ependymal lining of the ventricles are insensitive to pain. On the other hand, traction on or pinching or dilatation of, the intracranial arteries, veins or sinuses will cause pain. Pressure or traction on the trigeminal, glossopharyngeal or vagus nerves also may cause pain in the head.

*Site of the Pain.*⁴⁸—Pain arising from stimulation of the sensitive intracranial structures above the tentorium cerebelli is felt anterior to a vertical plane drawn between the ears and is transmitted by the trigeminal nerve. Pain arising from stimulation of intracranial structures below the tentorium is felt posterior to this plane and is transmitted by the glossopharyngeal nerve, the vagus nerve and the first three cervical nerves.

CLASSIFICATION OF HEADACHE

Headache may be divided into eight main types. The subdivisions of these main types are shown in table 1. We wish to emphasize that this classification is offered only as a working tool. It will unquestionably undergo considerable alteration as additional information is obtained on this subject.

TABLE 1 —CLASSIFICATION OF HEADACHE

- I Vasodilating headache
 - A Primary vasodilating headache
 - 1 Febrile diseases
 - a Acute infectious diseases
 - b Virus diseases
 - c Septis

- 2 Tension headache
- 3 Migraine
- 4 Histaminic cephalgia (Horton's syndrome)
- 5 Summer headache
- 6 Protein shock
- 7 Heat exhaustion
- 8 Effort headache
- B Decreased vascular tone
 - 1 Hypotension
 - 2 Anoxemia
 - a Anemia
 - b Pulmonary disease
 - c Carbon dioxide poisoning
 - 3 Neurasthenia
 - 4 Headache due to oversleeping
 - 5 Certain drug intoxications
 - 6 Fatigue
 - 7 Hunger
 - 8 Postanesthetic headache
 - 9 Addison's disease
 - 10 Acidosis
- C Increased pulse pressure
 - 1 Aortic regurgitation
 - 2 Arteriovenous fistula, if large enough to produce cardiac failure
 - 3 Hypertension
 - 4 Thyrotoxicosis
 - 5 Digitalis intoxication
- D Congestion of veins of head
 - 1 Coughing
 - 2 Hiccapping
 - 3 Mediastinal tumor
 - 4 Sinus thrombosis
 - 5 Tricuspid stenosis
 - 6 Failure of right side of heart
 - 7 Venous occlusion
 - a Superior vena cava
 - b Jugular veins
 - 8 Cervical adenitis
- II Direct involvement of vascular walls
 - A Inflammation
 - 1 Arteritis
 - a Temporal arteritis
 - b Panarteritis meningitis
 - B Degenerative diseases arteriosclerosis
 - C Hemorrhage
 - D Thrombosis (during the thrombotic process)
 - E Embolism
 - F Syphilis
 - G Multiple sclerosis
 - H Toxemia of pregnancy
 - I Uremia
- III Mechanical headache
 - A Space-occupying intracranial lesions
 - 1 Tumor

2. Abscess
- 3 Cyst
- 4 Granuloma
- 5 Aneurysm
- 6 Arteriovenous fistula
- B Secondary hydrocephalus
- C Hematoma of scalp
- D Lesions of skull
 - 1 Tumor
 2. Inflammation
 - a. Periostitis
 - b Osteomyelitis
 - c. Osteitis
 - 3 Necrosis
- E. Lumbar puncture headache
- IV Psychogenic headache
- V Neuropathic headache
 - A Neuralgia
 - 1 Trigeminal neuralgia
 - a. Ophthalmic
 - b. Maxillary
 - c. Mandibular
 - 2 Glossopharyngeal neuralgia
 3. Vidian neuralgia
 4. Sphenopalatine neuralgia
 - 5 Neuralgia of tympanic plexus
 - 6 "Cervico-occipital" neuralgia
 - B Neuritides
 - 1 Inflammatory
 2. Degenerative
- VI Headache due to lesions of extracranial structures
 - A. Muscular lesions
 - 1 Muscular tension headache
 2. Myositis
 - 3 Fibrositis
 - 4 Myofibrositis rheumatic headache (indurative headache)
 - B Lesions of neck
 - 1 Arthritis (including Pott's disease of the cervical vertebrae)
 2. Hypertrophic pachymeningitis of the cervical spinal cord
 - 3 Tumor
 - a. Neck
 - b. Cervical segment of vertebral column
 - c. Cervical spinal cord
 - C. Ocular lesions
 - 1 Glaucoma
 2. Iritis
 - 3 Corneal ulcer
 - 4 Retrobulbar neuritis
 - 5 Blepharitis
 - 6 Hordeolum
 - a. Internum
 - b Externum
 - 7 Chalazion
 - 8 Conjunctivitis

- 9 Dacryocystitis
- 10 Imbalance of extra-ocular muscles
 - a Primary
 - b Secondary to fatigue
- 11 Nystagmus
- 12 Light sensitivity
- D Lesions of ear
 - 1 Lesions of external auditory meatus
 - a Impacted cerumen
 - b Furuncle
 - c Foreign body
 - d Neoplasm
 - 2 Cholesteotoma
 - 3 Otitis media
 - 4 Otitic sclerosis
 - 5 Closure of eustachian tube
 - 6 Labyrinthitis
 - 7 Menière's syndrome
- E Lesions of nose
 - 1 Infection
 - 2 Allergic rhinitis
 - 3 Neoplasm
 - 4 Abnormalities of growth or development
 - a Bony spurs
 - b Deviation of septum
 - c Hypertrophy of turbinates
 - 5 Epistaxis
 - 6 Foreign bodies
 - 7 Disease of paranasal sinuses
 - a Infection
 - b Allergy
 - c Vacuum
 - d Neoplasm
 - e Occlusion of ducts
- F Lesions of throat
 - 1 Adenoids
 - 2 Pharyngeal tonsils
 - 3 Infection
 - a Tonsillitis
 - b Peritonsillar abscess
 - c Retropharyngeal abscess
 - 4 Lesions of base of tongue
- G Lesions of teeth
 - 1 Caries
 - 2 Abscess
 - 3 Pulpitis
 - 4 Osteomyelitis of jaw
 - 5 Malocclusion resulting in dislocation of temporomandibular joint
- H Trauma
 - 1 Contusion
 - 2 Concussion
 - 3 Fracture
 - 4 Dislocation of the temporomandibular joint

VII Reflex headache

A. Vagal irritation

- 1 Gastro-Intestinal dysfunction
2. Disease of liver

B Irritation of buccal mucosa

C. Constipation

D Menstruation

E Winter headache

F Carcinoma of the tongue and nasopharynx

G Utero-ovarian lesions

1 Displacement

2 Tumor

3 Inflammation

VIII Mixed types of headaches

Vasodilating Headache—This type of headache is caused by dilatation of the arteries or veins. The dilatation may be either extracranial or intracranial. The speed with which the dilatation develops has a significant bearing on the intensity of the headache.

Headache Due to Direct Involvement of the Vascular Walls—The best example of this type of headache is that which occurs in association with temporal arteritis. Although this type of headache is present constantly, it has a tendency to become more severe at night.

Mechanical Headache—This type of headache is the result of traction or pressure on structures that are sensitive to pain. A tumor of the brain may cause such a headache. In cases of tumor of the brain, headache occurs about as frequently without increased intracranial pressure as it does in association with an increase in intracranial pressure. Surgical removal of tumor of the brain has been recorded in cases in which the patients never have suffered from headache.

Psychogenic Headache—Psychogenic headache is a hallucination, not a physical reality. The characteristic feature of this type of headache is that it is invariable in intensity and distribution throughout the waking hours, but it never wakens the patient.

Neuropathic Headache—This type of headache is due to direct irritation or involvement of sensitive nerve trunks.

Headache Due to Involvement of Extracranial Structures—Involvement of any of the extracranial soft tissues of the head may cause headache.

Reflex Headache—This type of headache is best exemplified by the headache that occurs in association with constipation or menstrual disturbances. It is thought often to be due to extracranial irritation, direct or indirect, of nerves which carry cerebral vasodilator fibers.⁴

Mixed Types of Headache—Two or more types of headache may be present. The combination that is encountered most frequently is migraine and nervous tension headache.

TREATMENT

In the treatment of any type of headache, the objective of the physician should be twofold: first, to alleviate the pain during the attack and, second, to prevent subsequent attacks. Rational therapy depends on the recognition of the type of headache and the mechanism of production of the pain. Headache as an abstract problem and headache in a specific case are not one and the same thing. In the treatment of headache, one must consider the manifestations of the disease in a specific case; in other words, he must treat the patient, not merely the disease.

The treatment of headache should be both specific and supportive. It should be directed toward one of the following objectives: (1) to remove the stimulus which incites the mechanism resulting in pain, (2) to neutralize the stimulus, (3) to inhibit the mechanism that causes the pain or (4) to neutralize the pain. Treatment that only dulls the perception of the pain is symptomatic.

The scalp and the dura derive their blood supply chiefly from the branches of the external carotid artery while the pia mater and the brain are supplied by branches of the internal carotid artery.¹⁵ When the external carotid artery and its branches are constricted by a vasoconstricting drug, the internal carotid artery and its branches tend to be dilated.^{21, 48} This is a compensatory mechanism which insures an adequate blood supply for the brain. It has been designated the "middle meningeal reflex."²¹

In the treatment of vasodilating headache, the selection of a vasoconstricting agent depends upon the site of the vasodilatation. If the vasodilatation is situated in the external carotid artery or any of its branches, epinephrine,^{7, 41} posterior pituitary,⁴⁸ pitressin,^{41, 48} ergotamine tartrate,^{1, 3, 12, 22, 29, 33, 37} or dihydroergotamine (DHE-45)²⁸ will be effective. If the dilatation is situated in the internal carotid artery or any of its branches, ergotamine tartrate, oxygen^{2, 15} or dihydroergotamine²⁸ should be administered.

The following steps are of value in determining the source of the headache. Direct observation will reveal whether or not any of the vessels of the scalp are dilated. In case any of these vessels are dilated, exerting pressure that is sufficient to eradicate the pulsation in an involved vessel will relieve, in part or in full, all pain that is being caused by dilatation of the particular vessel.^{3, 26, 29, 33} If the vessels of the scalp are not involved, or if other vessels also are involved, epinephrine should be administered. This will relieve

headache that is due to dilatation of the vessels of the scalp or dura, but it will not relieve headache that is due to dilatation of the vessels of the pia mater and brain, in fact, it may produce headache by causing dilatation of these vessels.⁴¹ If epinephrine fails to relieve the pain, it may be assumed that the headache is due to involvement of the vessels of the pia mater or brain. In this case, ergotamine tartrate⁴¹ or dihydroergotamine should be administered. This diagnostic procedure is only of value early in the course of vasodilating headache, that is, before edema of the vascular wall has developed.

After the source of the pain has been determined, the choice of a therapeutic agent is simple. If an adequate dose of the selected vasoconstrictor is administered early in the course of the attack, the pain will be relieved in the great majority of cases. The degree of constriction that is produced depends on the concentration of the vasoconstricting drug in the circulating blood at one time, not upon the total dose that is administered in a given period. The effective dose also depends on the method of administration. It not only will vary in different cases but also may vary during different attacks in the same case.

The prompt intravenous administration of 0.5 to 1.0 c.c. of a 1:100,000 solution of epinephrine hydrochloride has proved effective in our hands. In cases of prolonged chronic headache, the results are more effective if the drug is administered by the drip method than they are if it is administered in a single dose. When we administer epinephrine hydrochloride by the drip method,²⁸ we use a 1:1,000,000 or 1:500,000 solution of the drug in physiologic salt solution. The solution usually can be administered at the rate of 20 to 50 drops per minute for at least an hour and a half.

By using a face mask, pure oxygen may be administered by inhalation. In some cases the administration of oxygen may have to be continued for several hours. Oxygen often is effective if it is administered early in the course of the attack. It may abort an attack of migraine or shorten it considerably.²

Ergotamine tartrate has been administered as a prophylactic in cases of migraine.¹ It usually is administered in tablets of 1 mg each three times daily. Some authors recommend placing two of these tablets under the tongue in the prodromal stage of migraine to abort the attack. This method of treatment has been successful in some cases.

One of us (B. T. H.) Peters and Blumenthal²⁸ made a comparative study of the effects of dihydroergotamine and ergotamine tartrate. This study indicated that dihydroergotamine is just as effective as ergotamine tartrate in the treatment of acute migraine. Neither

dihydroergotamine nor ergotamine tartrate will prevent the occurrence of future attacks. Toxic reactions occurred three times more frequently with ergotamine tartrate than they did with dihydroergotamine. This drug does not affect the blood pressure or the uterus. Hartman²⁸ recently obtained similar results with this new drug.

Histaminic cephalgia is the most severe type of headache that we have encountered. We have observed many cases in which an agonizing attack of histaminic cephalgia disappeared within one minute after the intravenous administration of 1 cc of dihydroergotamine. We also have observed the same response after the intravenous administration of a combination of 1 c.c. of a 1:100,000 solution of epinephrine hydrochloride and a 3 cc of a solution of the suprarenal cortex that was prepared by Dr. Kendall in the Division of Biochemistry.

Although an appropriate vasoconstrictor will relieve an acute headache if it is administered in sufficient quantity and at the proper time, the prolonged administration of such an agent will not prevent the recurrence of similar attacks.

Vasodilating Agents—Vasodilating agents are of value in the treatment of myositic, fibrositic and rheumatic headache. Myositic and fibrositic headache is due to the action of a local accumulation of metabolites on the endings of sensory nerves. Vasodilating agents increase the blood supply and thus aid in the removal of metabolites. Histamine and nicotinic acid⁴⁷ have proved effective in the treatment of this type of headache. A 1:250,000 solution of histamine base may be administered by the intravenous drip method for one to two hours. An accumulation of metabolites affects capillary permeability and causes edema of the affected muscles; consequently, vasodilating agents may increase the severity of the pain before they relieve it.

Nicotinic acid may be administered intravenously in physiologic salt solution. When it is administered by the intravenous drip method, the dose is 50 to 100 mg. When the subcutaneous method of administration is employed, the initial dose should be 25 mg. and each succeeding dose should be increased by 5 mg. until a dose of 100 mg. is reached.⁴⁷ Injections are given twice daily in this method of treatment.

Butler and Thomas¹¹ recently reported that the administration of histamine by the intravenous drip method was curative in cases of migraine. They employed a 1:500,000 solution of the drug in physiologic salt solution. The administration was started at the rate of 5 drops per minute but the rate was increased gradually. The results that we have obtained with this method of treatment have not been as satisfactory as those reported by Butler and Thomas.

In some of our cases the frequency, duration and intensity of the attacks were decreased but the attacks eventually recurred

As far as we have been able to determine desensitization by subcutaneous administration of histamine diphosphate is the only treatment that is effective in preventing subsequent attacks of histaminic cephalgia. In our experience, this syndrome does not respond to treatment with nicotinic acid. In cases of histaminic cephalgia, histamine desensitization is produced by the following method²⁵⁻²⁷. We use a solution containing 0.275 mg. of histamine diphosphate per cubic centimeter. Solutions of this strength are readily obtainable on the drug market. The solution is administered twice daily (at 8 A.M. and 4 P.M.) in the following doses: first dose, 0.10 c.c., second dose, 0.15 c.c., third dose, 0.20 c.c., fourth dose, 0.25 c.c., fifth dose, 0.30 c.c., sixth dose, 0.35 c.c., seventh dose, 0.40 c.c., eighth dose, 0.45 c.c., and ninth dose, 0.50 c.c. In some cases a dose of 1 c.c. has been necessary. We never have administered more than 1 c.c. of this solution at one time. If, at any time, the patient notices slight flushing of the face or any other symptoms that are indicative of a subjective or objective response to the administration of the drug, the next dose should be reduced 50 per cent and the subsequent doses should be increased gradually as just described. After the attacks have disappeared, it often is necessary to administer a maintenance dose for an indefinite period in order to prevent recurrence of the attacks. We have found it necessary to alter the routine to fit the needs of the individual patient. Some patients do not require a maintenance dose. Hapamine (histamine azoprotein)¹⁹ also has been used for histamine desensitization but it does not appear to be as effective as histamine diphosphate.

Potassium thiocyanate is of value in the treatment of hypertensive headache and in the prevention of attacks of migraine^{12, 24, 28}. When it is used to prevent attacks of migraine, the concentration of the drug in the serum should be maintained at 10 to 12 mg. per 100 c.c.²⁴. The drug relieves hypertensive headache by lowering the blood pressure. It is of particular value in cases in which hypertensive headache is associated with migraine. In cases in which hypertensive headache occurs alone, the pain may be relieved by elevating the head of the bed 14 inches (35.5 cm.). Potassium thiocyanate also may be administered in cases in which migraine occurs alone. In such cases the concentration of the drug in the serum should be maintained at 4 to 8 mg. per 100 c.c.²⁴. Thiocyanates are toxic substances. When these drugs are administered in cases of headache, one should take the same precautions that are employed when they are used in the treatment of hypertension. The concentration of the drug in the serum should be determined at frequent

intervals and the patient should be observed carefully for the development of toxic manifestations or manifestations of an idiosyncrasy. Toxic manifestations produced by administration of thiocyanates are similar to those produced by the iodides and may include toxic psychosis. Thiocyanates have a toxic action on smooth muscle.

The literature contains reports of cases in which acute attacks of vasodilating headache have been relieved by the administration of such vasodilating substances as histamine,¹¹ nicotinic acid,^{4, 5} and thiocyanates.¹² These substances are effective in cases in which the prodromal stage of the headache is associated with vasospasm. The only way to determine their effectiveness in a given case is to try them. When thiocyanate is used intravenously, its sodium salt is administered in a concentration of 0.83 per cent in physiologic salt solution. The maximal single dose of this salt is 2 gm. Angina pectoris may be a manifestation of an idiosyncrasy to thiocyanates. The solution should be administered slowly and the patient should be observed during the administration and for at least an hour and a half thereafter.

Diet.⁴²—Diet has a definite place in the treatment of headache. It is well known that hunger can cause headache. Hunger also can aggravate the pain in the head.

Dextrose.—Intravenous administration of a 50 per cent solution of dextrose serves several purposes in cases of headache. It is an effective antinauseant in cases in which headache is associated with nausea and vomiting and in cases in which the administration of ergotamine tartrate or dihydroergotamine causes nausea and vomiting. Dextrose is a dehydrating agent and it may help to relieve the edema of the vascular walls which is associated with prolonged vasodilatation. Intravenous administration of 50 c.c. of a 50 per cent solution often will relieve much of the nausea and vomiting associated with migraine. As hypertonic solutions of dextrose draw fluid into the vascular bed, they should be used with caution in cases of pulmonary congestion and in cases in which the cardiac function is poor.

Vitamins—Vitamin A is of value in the treatment of headache that is due to sensitivity to light.²⁶ The intramuscular administration of 25,000 units of vitamin A is of particular value in the treatment of this type of headache. The administration of this dose should not be continued for more than seven days. Headache that is due to sensitivity to light occurs much more frequently than is generally recognized.

Thiamine often is of value in the treatment of neuropathic headache. Thiamine deficiency causes arteriolar dilatation and may be

one of the factors responsible for vasodilating headache. The therapeutic dose of thiamine is 10 to 50 mg. It may be administered orally, intramuscularly or intravenously.

Riboflavin deficiency is associated with photophobia. In some cases in which headache is due to sensitivity to light, a combination of riboflavin and vitamin A is more effective than vitamin A alone. The therapeutic dose of riboflavin is 2 to 15 mg for oral administration.

Nicotinic acid not only is of value in vasodilating headache⁵ but also in neuropathic and muscular headache.⁴⁷ The fact that nicotinic acid (but not its amide) is a vasodilating agent may be of greater importance than its effect on carbohydrate metabolism in the treatment of headache. The maximal single dose of nicotinic acid is 100 mg. It may be administered by any route.

Pyridoxine (vitamin B₆) has been reported to be of value in the treatment of hyperemesis gravidarum. It is possible that this vitamin might be effective in the treatment of the nausea and vomiting of migraine.

Vitamin C is a naturally occurring antihistamine substance. It augments the action of epinephrine. Two hundred milligrams of this vitamin may be administered by any route and repeated at stated intervals.

Calcium.^{1, 20, 37}—Calcium deficiency causes hyperirritability of all types of nerve. Calcium acts as an antispasmodic on smooth muscle; at the same time it increases the tonus and contractile power. It is of value in the treatment of vasodilating headache. It may be administered orally in the form of tablets or a 10 per cent solution of gluconate may be administered intravenously.

Antidiuretics—In the treatment of migraine, some physicians have obtained good results by administering micapon. This is an antidiuretic which consists of a mixture of potassium chloride and calcium lactate. It is marketed in the form of tablets. Each tablet contains 2½ grains (0.137 gm.) of potassium chloride and 2½ grains (0.137 gm.) of calcium lactate. The recommended dose is two tablets, three times daily.

Hormones^{1, 7, 12, 34, 37}—Extract of the suprarenal cortex increases the rate of gluconeogenesis. Some authors have expressed the opinion that it has an antihistaminic action. When this drug is administered in a case in which histamine is being administered intravenously it does not counteract the effects of the histamine. In cases of severe histaminic cephalgia in which the attacks occur every night or even more frequently the intravenous administration of cortical extract twice a day may reduce the frequency of the attacks. The role of this substance in decreasing the frequency of

the attacks of histaminic cephalgia is not understood. In cases of histaminic cephalgia in which large doses of histamine have been administered, the patients may be so sensitive to the drug that the usual procedure of histamine desensitization cannot be instituted promptly unless cortical extract is administered while histamine desensitization is being carried out. The administration of cortical extract should not be continued indefinitely. Any unique value it may have in the treatment of histaminic cephalgia is obtained early in the course of treatment.

Hormonal deficiency is the only indication for administration of hormones. In some cases of migraine, the disease is aggravated by pituitary or ovarian dysfunction. In appropriate cases, solution of posterior pituitary or estrogen may be of value.

Analgesics.^{7, 29}—The salicylates are effective in the treatment of headache associated with myalgia, cervical arthritis and myositis, fibrositis or myofibrositis of the scalp. In cases of febrile headache, they are specific if they are effective as antipyretics. If the pain is not intense, their central depressant action may be sufficient to dull its perception. Rheumatic headache always will respond, at least partially, to administration of salicylates^{6, 40}.

The coal-tar antipyretics, acetanilid and acetophenetidin, are more potent analgesics than the salicylates and they also are more toxic. The habitual use of these drugs may cause anemia, loss of weight, anorexia, fatigability, gastro-intestinal disturbances, insomnia, circulatory asthenia and a whole train of so-called functional disorders, which themselves may be a predisposing cause of headache.

Aminopyrine and antipyrine have been condemned because agranulocytosis occasionally follows the administration of aminopyrine. Although this reaction does not develop unless a patient is hypersusceptible to the drug, repeated administration of the drug may result in the development of hypersusceptibility.

Sedatives.^{7, 29}—In the treatment of headache, sedatives are used chiefly to break a vicious cycle which starts with hyperirritability. Once this has been accomplished, the indication for sedation ceases. The tendency to administer sedatives for a prolonged period in cases of psychogenic headache is both lazy and dangerous. In cases of this type of headache, the underlying hysteria, neurosis, psychoneurosis or psychosis should be treated.

Barbiturates augment the action of analgesic drugs. Large doses of the barbiturates produce depression of the vasomotor center and cause peripheral vasodilatation and hypotension. The barbiturates have a tendency to cause dilatation of the cerebral vessels but this action varies according to the barbiturate that is administered. It

should be remembered that barbiturates depress the proprioceptive mechanisms which regulate vasomotor tone. As a result, they may, and frequently do, aggravate vasodilating headache. In the treatment of headache, the barbiturates are of value chiefly as soporifics.

Bromides^{8 29 40 42} were a favorite headache remedy for a long time. They depress the central nervous system and are effective sedatives. These drugs may be of value in cases in which anxiety is an etiologic factor. Bromides do not depress vascular tone as do the barbiturates. The dose of the bromides depends on the individual patient. When these drugs are prescribed, the physician should be on the alert for signs of bromidism.

Narcotics—Narcotics are contraindicated in the treatment of chronic headache. Their use in the management of headache is justified in cases of inoperable brain tumor or other terminal disease.

Cannabis Indica.^{1 41}—Some authors have recommended the use of cannabis indica in the treatment of migraine. This drug is habit forming and it has both a depressing and exciting action on the central nervous system. It seems unwise to administer this type of drug in cases of migraine.

Hypoglycemic Reactions—It has been reported that the induction of hypoglycemic reactions by administration of insulin is of value in the treatment of acute migraine.^{15 45} The effect produced by the insulin may be equivalent to that produced by intravenous administration of histamine as the concentration of blood histamine increases as the concentration of blood sugar decreases.⁹

Antihistamine Substances.—In some cases of histaminic cephalgia, oral doses of histaminase in large amounts may be effective prophylactically. Benadryl (beta dimethylaminoethyl benzhydryl ether hydrochloride) is the most potent antihistamine substance that has been developed thus far for administration to human beings. In our experience, the intravenous administration of this preparation has aborted both induced and spontaneous attacks of acute histaminic cephalgia in a few cases.⁴⁷ Clinical experience with this drug in the treatment of headache is still too limited to warrant an evaluation of its potentialities at this time. Pyribenzamine (N'-pyridyl-N'-benzyl-N-dimethyl-ethylenediamine monohydrochloride) is another antihistamine substance that has just been released for clinical investigation. Our work with this drug suggests that it may be of value in the treatment of some types of allergy. Whether or not it will be of value in the treatment of headache remains to be determined.

PT-8 (beta 2-pyridyl ethyldiethylamine hydrochloride) PT-9

(beta 2-pyridyl ethylmethylamine hydrochloride), PT-10 (1,2-pyridyl 2, methylaminopropane hydrochloride) and PT-11 (beta 2-pyridyl ethylamine hydrochloride) are additional antihistamine substances that have been used clinically. Of these four substances, PT-9 has been most valuable in the treatment of headache. Although these drugs may be effective in an occasional case of headache, the results of their administration have not been as uniform as those produced by the subcutaneous administration of histamine diphosphate.

With the exception of histaminase (an enzyme obtained from the mucous membrane of the small intestine and desiccated kidneys of hogs) and benadryl, none of these substances is available commercially at the present time. They probably will not be released until further clinical investigation yields more conclusive data.

Heat and Massage.^{6, 40}—Dry heat and massage are particularly valuable in the treatment of myositic, fibrositic and rheumatic headache as they improve the circulation of the involved tissues.

Nerve Block.^{7, 14, 85}—Nerve block with a local anesthetic has proved of value in cases of acute headache. In some cases of unilateral headache, the pain has been relieved by blocking the cervical sympathetic ganglia. In other cases, headache has been relieved by blocking the trigeminal nerve or the sphenopalatine ganglion. In one case which we have observed, the pain of abdominal migraine was relieved on two occasions by blocking the twelfth thoracic and first lumbar ganglia on both sides. Nerve block may be of value in any case in which the nerve that transmits the pain or the nerve that carries motor fibers for the pain-producing mechanism is accessible. Its effectiveness in a given case can be determined only by trial.

Lumbar Puncture and Phlebotomy.—Lumbar puncture often will relieve mechanical headache that is associated with increased pressure of the cerebrospinal fluid. Unless the cause of the increased pressure is removed, the headache will recur. In certain cases in which mechanical headache is due to venous congestion, the pain can be relieved by phlebotomy, although headache alone is not sufficient indication for this procedure. Phlebotomy also will relieve headache associated with polycythemia vera.

Supportive Treatment.—In the treatment of any type of headache, body tonus should be maintained, the diet should be adequate and the patient should obtain physical and mental rest. Excessive tonus is the first indication of physiologic strain. Loss of tonus is evidence of definite dysfunction.¹⁴ If this is not corrected a pathologic change will develop.

Explanation to Patients.—In any case of chronic or periodic

headache the mechanism of the attack should be explained to the patient. In every case of periodic headache, there is a fear complex of greater or lesser degree. Although some patients will not admit it, they frequently fear that they have a tumor of the brain. Fear of the attack lowers the pain threshold. Patients are often confused and even bewildered as to the nature of their headache. Frequently they have consulted many physicians and have received conflicting reports and advice. The average patient is intelligent enough to appreciate a simple explanation of the problem and this may accomplish as much, and sometimes more, than the medicine which one employs. A mental cathartic often serves a useful purpose.

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THE PROBLEM OF BLACKOUT AND UNCONSCIOUSNESS IN AVIATORS

EDWARD H LAMBERT AND EARL H WOOD

BEFORE World War II engineering skill had increased the speed and maneuverability of airplanes to the point that their military effectiveness was limited by the inability of the pilot to withstand the forces developed in combat maneuvers. The sudden change in direction of flight which occurred in sharp turns and when pulling out of dives at high speed produced centrifugal force of such magnitude that the pilot was often rendered temporarily blind (blackout) or unconscious and unable to control his aircraft. It was recognized that if a pilot could be rendered resistant to centrifugal force, he would have a tactical advantage over his adversary. This situation posed two problems for medical research: first, to determine the physiologic basis for the pilot's failure when exposed to centrifugal force and second, to develop means to improve safely his ability to withstand the force.

During the decade preceding the war the most significant research in this field was conducted in Germany. Relatively little was accomplished elsewhere. This is amply illustrated in Ham's review¹ of the reports on centrifugal force which had been published up to 1943. After the outbreak of the war military and civilian laboratories devoted almost solely to the problem of centrifugal force appeared in quick succession in Canada, the United States and Australia. As in other war projects these laboratories conducted their investigations in secrecy. While the results of their researches have been gratifying both from a scientific and from a military point of view little of the information obtained has yet been published in medical journals.² It is the purpose of this paper to introduce the physician to some of the unique physiologic effects of centrifugal force on the human being and the means which have been devised to counteract these effects in the aviator.

THE NATURE OF CENTRIFUGAL FORCE

Travel at a sustained high speed has no effect on an aviator enclosed in his aircraft as long as the path of flight follows a straight line. Unless the pilot can see the ground or objects hurtling by he has little or no sensation of motion. However the pilot becomes immediately conscious of a change in the direction of flight. In a

banked turn or in a pullout from a dive, he is pressed into his seat as a result of the centrifugal force induced by motion in a curved path. The amount of the force is determined by the speed of the plane and its radius of turn according to the equation, Force (in g units) $= \frac{V^2}{32r}$, in which V is the velocity in feet per second and r the radius of turn in feet. The magnitude of the force is commonly expressed in multiples of the earth's gravitational force, that is, in g units. Thus expressed, the effect of the force becomes readily apparent. *Centrifugal force increases weight.* If the pilot has a weight of 150 pounds (68 kg) due to the normal gravitational force of 1 g, he will have a weight of 300 pounds (136 kg) in a turn which develops a force of 2 g, 450 pounds (204 kg) at 3 g, 600 pounds (272 kg) at 4 g and so on. The pilot would experience a force of 4 g while making a turn with a radius of 1,500 feet (457 meters) at a speed of 300 miles (483 kilometers) per hour. If the turn were made in half this radius (750 feet [229 meters]), the force would be 8 g, while if the speed were doubled (600 miles [965 kilometers] per hour), the force would be 16 g.

It is evident that as the speed and maneuverability of aircraft are increased, the stress on the pilot rises very rapidly. Fighter planes used in the war were capable of generating centrifugal force in excess of 7 g during combat maneuvers. Exposed to a force of this magnitude the pilot weighs more than $\frac{1}{2}$ ton (454 kg). Each of his body tissues and fluids becomes correspondingly heavier and remains so as long as his plane continues to fly in a curved path. The blood becomes heavier than molten iron with the result that profound alterations in circulation occur. It is as a consequence of these circulatory changes that the pilot experiences blackout or unconsciousness.

THE HUMAN CENTRIFUGE

While the effects of centrifugal force on man may be studied in the airplane, accurately controlled observations in flight are difficult to make, time consuming and hazardous. Human centrifuges have been built to reproduce the centrifugal force of aerial maneuvers on the ground under laboratory conditions. The human centrifuge consists essentially of a superstructure which revolves in a horizontal plane about a central axis. At one end of the superstructure is a cockpit which is free to swing outward when the centrifuge is in motion. The resultant force acts in the direction from head to foot on the subject seated in the cockpit. The superstructure of the Mayo centrifuge is set in motion by clutching to a 40 ton rotating flywheel and is stopped by declutching and

applying a brake. The speed of rotation of the superstructure is controlled by the speed of the rotating flywheel or by the degree of engagement of the clutch so that the exact centrifugal force desired may be developed rapidly or slowly and maintained for any required period. At the subject's heart, 15 feet (4.5 meters) from the center of rotation, a force of 4 g is delivered when the cockpit travels at a speed of 30 miles (48 kilometers) per hour (28 revolutions per minute).

In our laboratory observations have been made on approximately 300 men in a total of 9500 exposures to centrifugal force. The greatest number of observations have been made using a force-time pattern in which the maximal g level was reached in two to three seconds and was maintained for fifteen seconds. This type of exposure has given the most complete picture of the effects of centrifugal force as the aviator may experience them. A smaller series of observations made by the same procedures on forty men in a specially instrumented dive bomber has indicated that the fundamental physiologic effects observed on the centrifuge apply equally well to the aircraft pilot.

SUBJECTIVE SENSATIONS OF CENTRIFUGAL FORCE

Man is accustomed to existence under a force of 1 g. When exposed to centrifugal force exceeding 1 g he has a feeling of increased weight. In the sitting position, pressure on the buttocks is increased and the arms and legs feel intensely heavy. The soft tissues of the body are drawn downward. This effect is particularly noticeable in the face and produces an appearance of great age (Fig. 119). As a consequence of the increase in weight of the body, movement becomes increasingly difficult the greater the magnitude of the force. At 2.5 g it is practically impossible to get up from a sitting position and at 4 g the arms and legs can barely be lifted. However, a well balanced sitting posture can be maintained at forces of more than 8 g, and the pilot is able to fly his aircraft at such forces provided he already has his hands and feet on the controls and is not rendered unconscious.

The foregoing phenomena of increased weight start with the very onset of the centrifugal force and are present until the force is removed. Disturbances of vision and consciousness do not occur until exposure to centrifugal force has been maintained for more than three seconds.

The changes in vision have been followed on the centrifuge by testing the subject's ability to respond to light signals placed in his peripheral and central fields of vision. Records of the subject's responses are used to confirm his own statement of his symptoms.

and to determine the time at which peripheral and central vision were lost. Subjects in a comfortable sitting posture experience dimming of the peripheral field of vision after at least three seconds' exposure to forces between 3.0 and 4.0 g. Loss of peripheral vision occurs at forces between 3.5 and 4.5 g and complete loss of vision between 4.0 and 5.0 g. Complete loss of vision occurs without disturbances of hearing or consciousness. This is true blackout. When the subject is exposed to a force which produces blackout, the visual disturbance commences with dimming of peripheral vision on the average after three seconds' exposure to the maximal force and



Fig. 119—Subject on the human centrifuge *a*, At 1 g prior to centrifugation *b*, At 5 g during centrifugation. Apparatus shown includes ear attachments for blood content of the ear and ear pulse and a mouthpiece for respiration.

progresses to loss of peripheral vision at the fifth second and to loss of central vision at the eighth second. The disturbances of vision are temporary, in fact, usually complete restoration of vision occurs after a few seconds even when the centrifugal force is maintained. In any case vision returns promptly when the force is terminated.

Diminution of hearing and loss of consciousness occur during exposure to forces 0.5 g or more above the level which produces blackout. As a rule, loss of consciousness occurs between the fourth and the sixth second of exposure to centrifugal force and is accom-

panied by relaxation of the musculature, allowing the head and body to slump and the hand to fall from the control stick. There is complete loss of orientation as to time and place. Even with immediate cessation of the force, disorientation lasts on the average for fifteen seconds and in some instances for as long as thirty seconds. The subject afterward frequently recalls having been dreaming although occasionally he is unaware that he has been unconscious. In roughly 50 per cent of cases mild to rather severe convulsive movements occur during the period of recovery.

THE EFFECT OF CENTRIFUGAL FORCE ON BLOOD PRESSURE

The immediate cause of blackout and unconsciousness is revealed by measurement of the arterial pressure at the level of the subject's head during the exposure to centrifugal force. Such measurements have been accomplished by puncture of the radial artery with the subject's wrist supported at head level in more than 250 centrifuge runs. At head level a pronounced fall of both systolic and diastolic pressure occurs with the onset of centrifugal force (Fig. 120). The pressure continues to fall on the average for a period of seven seconds after this time some recovery occurs even though the force is still maintained. The magnitude of the fall in blood pressure is proportional to the magnitude of the centrifugal force. On the average the decrease in systolic pressure amounts to 32 mm. of mercury for each g of increase in centrifugal force. In general, when no disturbance of vision occurs the systolic pressure at head level during the exposure to centrifugal force is found to have remained greater than 50 mm. of mercury. When complete loss of vision occurs, the systolic pressure has fallen to less than 20 mm. of mercury. When unconsciousness occurs, the systolic pressure has fallen to zero.

In sharp contrast to the pronounced fall of blood pressure at the level of the head, there is a relatively slight decrease in arterial pressure at heart level during exposure to centrifugal force. With the wrist supported at the level of the base of the heart the systolic pressure in the radial artery is reduced on the average only 5 mm. of mercury for each additional g of force and the diastolic pressure is practically unchanged. During the period of recovery which occurs while the force is maintained the pressure at heart level increases 20 to 70 mm. above the control value (Fig. 121).

The reason for the considerable difference between the pressure at head level and the pressure at heart level is readily apparent when the effect of centrifugal force on the weight of the blood is considered. In a man exposed to the normal force of gravity, or 1 g, a pressure of roughly 24 mm. of mercury is required to

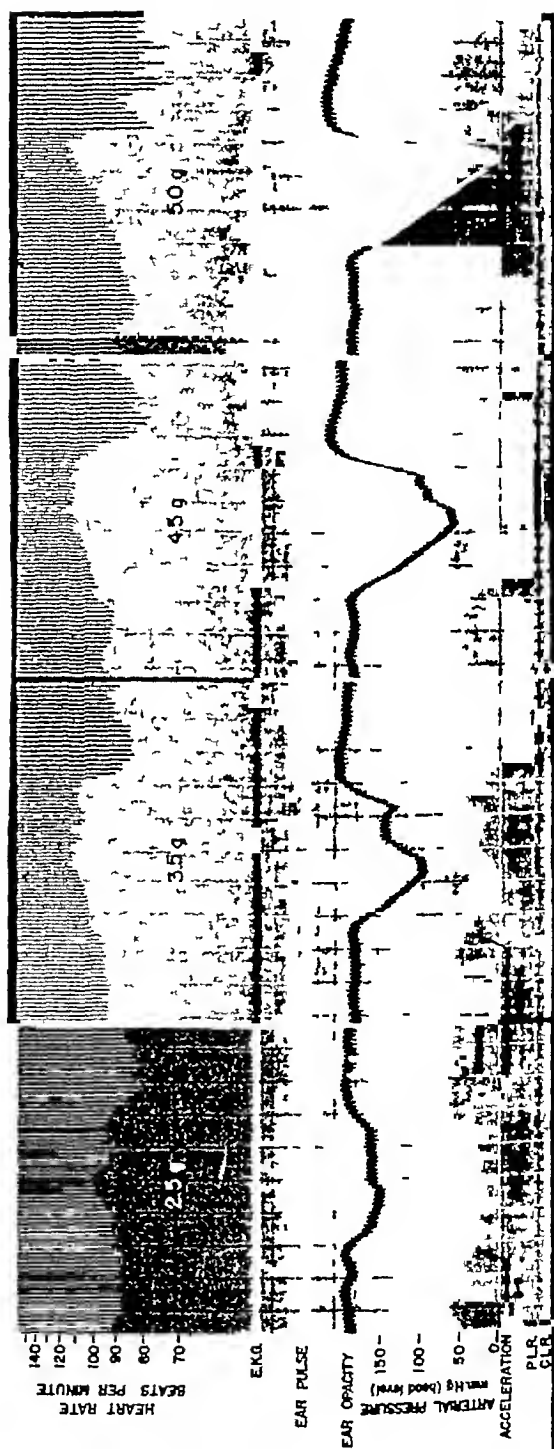


Fig 120—The blood pressure at head level and other variables during exposure to centrifugal force. The vertical white lines are five seconds apart. The black line labeled acceleration indicates centrifugal force in g units. A downward deflection of ear opacity indicates a decrease in blood content of the ear. P L R means peripheral light response. CLR means center light response and P L L means peripheral lights lost. An upward deflection occurs when the lights are turned on by the observer and a downward deflection when they are turned off by the subject.

raise the blood from the heart to the head, a distance of about 1 foot (0.3 meter). In other words, the blood pressure is 24 mm of mercury less at the head than at the base of the heart because of the hydrostatic distance between the two levels. At a force of 5 g on the centrifuge the weight of the blood is increased five times and a pressure of 120 mm of mercury is required to raise it to the head. It is clear that if the subject's systolic arterial pressure

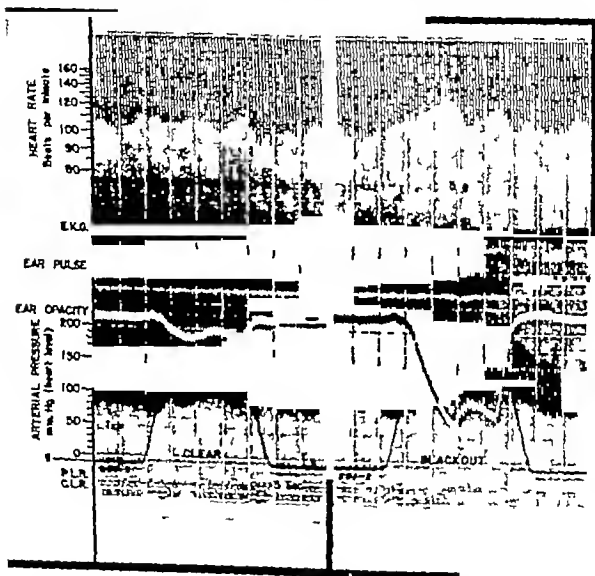


Fig 121 -The blood pressure at heart level and other variables during exposure to centrifugal force. For further explanation see legend of figure 120

at heart level) is 120 mm of mercury the pressure at head level during exposure to a force of 5 g will be zero and cerebral blood flow will cease.

Thus the principal factor responsible for the reduction in arterial pressure at the level of the head during exposure to centrifugal force is the increased weight of the blood column between the heart and the head. The reduction in pressure at head level due to this factor occurs at the moment the centrifugal force is applied.

A further smaller decrease in arterial pressure at both heart and head levels continues while the force is maintained. This is a consequence of the increased weight of the column of blood below the heart. In a sitting position at 5 g the blood pressure in a man's feet would be roughly 250 mm of mercury greater than that at the base of his heart. As a result of this sudden great increase of pressure, arterial blood flow to the dependent portions of the body may be increased. Simultaneously, pooling of blood will occur in the dependent veins. Both of these factors would tend to decrease arterial pressure.

The progressive decrease of arterial pressure which starts with onset of centrifugal force is checked after a period of seven seconds and is followed by some recovery of the arterial pressure while centrifugal force is maintained. This recovery of arterial pressure is due principally to the action of pressor reflexes (carotid sinus) which are initiated by the decrease in arterial pressure at head level. The rise of pressure not only checks the increasing severity of symptoms but, if sufficiently great, will result in recovery from symptoms.

It is of interest that vision is affected by less severe reductions in arterial pressure than is consciousness and that complete loss of vision may occur with arterial pressures at which no disturbance of consciousness is apparent. The explanation for this is that the effective arterial pressure in the eye is actually less than that in the brain. Circulation in the retina is opposed by a normal intraocular pressure of approximately 18 mm of mercury, while circulation in the brain is actually aided by a considerable negative pressure at this level because of the hydrostatic effect of the column of cerebrospinal fluid extending from brain to sacrum. Unique proof of the retinal origin of the visual symptoms is the fact that by applying 30 to 40 mm of mercury suction to the eyeball by means of a special mask, blackout during exposure to centrifugal force can be prevented. Similarly, applying 20 to 30 mm of mercury positive pressure to the eyeball will lower by 1 g the force necessary to produce blackout. The force necessary to produce unconsciousness is not altered by these procedures.

RELATED CARDIOVASCULAR EFFECTS

The fall and subsequent recovery of the arterial pressure at head level during exposure to centrifugal force set the pattern for other changes which may be observed in the cardiovascular system. By means of colored motion pictures, it can be seen that blood rapidly drains from the subject's face after onset of centrifugal force. The complexion becomes ashen and deathlike. This

effect reaches its maximum in eight to twelve seconds. After this, blood begins to return to the face even while the centrifugal force is maintained. An objective record of the changes in blood content of the tissues at head level has been obtained by photo-electric determination of variations in the amount of light which will pass through the ear. The magnitude of the decrease in blood content of the ear increases with the magnitude of the force to which the subject is exposed and bears a relatively constant relation to the visual symptoms which he experiences (Fig. 120).

Superimposed on these gross changes in blood content of the ear are the pulsations in ear volume which occur with each beat of the heart. By suitable electrical circuits this ear volume pulse can be isolated and amplified for accurate study. The ear pulse amplitude becomes reduced during exposure to centrifugal force and is zero when systolic arterial pressure is zero. Recovery of the amplitude of the ear pulse follows exactly the recovery of the systolic arterial pressure (Figs 120 and 121).

Rapid and marked changes in the heart rate occur during the exposure to centrifugal force (Figs 120 and 121). The heart rate starts to increase almost at the moment of onset of the centrifugal force and increases progressively until the compensatory reactions occur. Following the compensatory rise in arterial pressure, some slowing of the heart rate occurs. The maximal heart rate attained (120 to 180 beats per minute) is usually proportional to the decrease in arterial pressure.

The changes in the ear pulse, blood content of the ear and heart rate have afforded a valuable objective index to changes in circulation at the level of the head and have been used extensively for this purpose in determining the effectiveness of various antiblackout procedures and devices.

THE SEQUENCE OF EVENTS DUE TO CENTRIFUGAL FORCE

From the preceding discussion it is evident that the increased weight of the blood which occurs as a consequence of exposure to centrifugal force initiates a definite sequence of physiologic changes in man. The blood pressure at the level of the head falls, the heart rate increases, the blood content of the ear decreases, the amplitude of the ear pulse is reduced or lost and finally changes in vision or consciousness if they are to occur become evident. This period in which the pilot rapidly reaches his poorest physiologic state has been termed the period of progressive failure. The progressive failure is terminated as a rule by a compensatory reaction which becomes effective about seven seconds after the onset of the force. During the period of compensation the blood pressure

rises, the ear pulse improves, the amount of blood in the ear increases and the heart rate slows. If the compensation is sufficient, recovery from symptoms will occur. The recognition of these changes and the regularity of their occurrence has allowed an orderly and quantitative approach to the problem of protecting the aviator against the effects of centrifugal force.

ANTIBLACKOUT PROCEDURES AND DEVICES

The ability of the aviator to withstand centrifugal force can be increased in three principal ways: (1) by limiting the duration of the force, (2) by changing the position of the pilot to reduce the hydrostatic distances between the heart and head and (3) by increasing his arterial pressure.

I Limitation of the Duration of Force—Pilots can avoid blackout during turns and pullouts from dives by limiting the duration of the maneuver to less than the three to four seconds required for the development of symptoms due to centrifugal force. While commonly used, this procedure is dangerous. The pilot, to accomplish a turn in a limited time, must make the maneuver violent and may overstress his plane. Furthermore, should he underestimate the duration of the force by a second or two, unconsciousness with its attendant dangers will result.

II Change in the Position of the Pilot—If the pilot assumes a prone or supine position in his plane, the vertical heart-to-brain distance becomes zero and centrifugal force, acting transversely to the long axis of the body, causes no decrease in arterial pressure at the head. In this position man can withstand sustained forces in excess of 12 g without the occurrence of visual symptoms or unconsciousness. While this constitutes an effective means of avoiding blackout, it has not been used because of practical difficulties of plane design and of piloting the plane. However, pilots can accomplish some shortening of the vertical heart-to-brain distance by crouching in their seats during the exposure to centrifugal force. This procedure was used extensively by German pilots.

III Procedures which Increase Blood Pressure—The pilot's resistance to centrifugal force can be increased by increasing his arterial blood pressure. There are three principal ways in which this may be accomplished: (1) by voluntary straining maneuvers which produce a pressor effect, (2) by suits which apply pressure to the dependent portions of the body, and (3) by drugs which produce a pressor effect. All three methods are effective in increasing g tolerance, but only the first two have been used widely.

Pilots have used self-protective, straining maneuvers more than

any other single procedure or device to prevent blackout. Some of the straining procedures used by veteran pilots have been selected and refined on the basis of centrifuge studies to produce a very effective maneuver. This consists essentially of a series of rapidly repeated forced expirations against a partially closed glottis coordinated with muscular straining. By proper use of this maneuver many persons have been able to maintain clear vision during sustained exposures to 9 g. The chief objection to the use of such maneuvers is that they unavoidably decrease the pilot's efficiency and increase fatigue.

The principal efforts of centrifuge laboratories in the past few years have been directed toward the development of simple devices which would increase the resistance of pilots to centrifugal force but would not require the attention of the pilot nor restrict his activity in combat. This was achieved by the development of the so-called antiblackout suits. These suits have been designed to apply pressure to the dependent parts of the body by means of air bladders placed over the calves, thighs and abdomen. Pressure control valves actuated by centrifugal force automatically regulate the pressure in the bladders according to the magnitude of the force. The restrictions which this pressure imposes on circulation below the heart result in an increase of the arterial pressure at heart level which is available during exposure to centrifugal force to maintain circulation to the head. Suits have been constructed which can increase the pilot's tolerance to centrifugal force by 1 to 3 g, depending on the design of the bladder system and the amount of pressure applied.

To meet the practical needs of pilots of conventional fighter aircraft in World War II it was found that a very simple pneumatic bladder system which would afford 1 to 1.5 g protection against blackout was satisfactory. Such a bladder system was incorporated in lightweight, comfortable garments. These suits became standard equipment for fighter pilots in both the Army and the Navy. Combat reports have given conclusive evidence that these suits afforded our pilots a definite margin of superiority.

Antiblackout suits, especially of this simple type, are not the final answer to the problem of prevention of blackout in aviators. Since centrifugal force is proportional to the *square* of the velocity it can be predicted that with the advent of superspeed planes the present antiblackout suits will be as obsolete as the planes in which they were designed to be used. Additional physiologic investigations are necessary before methods can be developed which will enable pilots to utilize fully the potentialities of these new aircraft.

REFERENCE

- 1 Ham, G C Effects of centrifugal acceleration on living organisms War Med 3 30-56 (Jan) 1943
- 2 Reports dealing with the topics discussed in this paper unfortunately have not yet been published and direct references therefore cannot be given. Although the data on which this report is based were collected for the most part in the Acceleration Laboratory of the Mayo Aero Medical Unit, ideas and results have been freely exchanged between all of the laboratories working in this field in the United States and the British Empire throughout the war period. Important contributions have been made by many investigators and, although specific references cannot be given to their reports, we wish to acknowledge the great assistance which their work has afforded in the compilation of this review. Investigators of the blackout problem have been principally associated with the following centrifuge laboratories
 - 1 Royal Canadian Air Force Accelerator Unit, Toronto, Canada
 - 2 U S Army Aero Medical Laboratory, Wright Field.
 - 3 University of Southern California, Los Angeles, California
 - 4 U S Navy, Pensacola, Florida
 - 5 Mayo Aero Medical Unit, Rochester, Minnesota

CLINICAL USE OF THIOURACIL*

SAMUEL F HAINES AND F RAYMOND KEATING, JR.

SINCE H S Plummer introduced strong solution of iodine (Lugol's solution) in the treatment of exophthalmic goiter in 1922, the administration of iodine followed by subtotal thyroidectomy has become the method of choice for dealing with this disease. The recent advent of goitrogenic drugs, of which thiouracil has had the most extensive trial, represents a distinct advance in knowledge of the physiology of the thyroid and a radical innovation in therapeutic methods.

In the past three years widespread use has produced a considerable volume of information regarding the use and limitations of thiouracil in the treatment of hyperthyroidism. Insufficient time has elapsed, however, for conclusive evaluation of its usefulness in relation to administration of iodine or to surgical treatment of hyperthyroidism. There has not been time, for example, for adequate appraisal of the permanence of remissions of exophthalmic goiter induced by thiouracil alone or of the effects its use may have on the morbidity and mortality rates following subtotal thyroidectomy for this condition. Nevertheless, regardless of whether thiouracil continues to be the antithyroid drug of choice, or whether as may be, it is eventually replaced by one or another of the hundreds of similar compounds being studied, it is apparent that a new and important tool in the management of hyperthyroidism has appeared on the scene.

PHYSIOLOGIC OBSERVATIONS

MacKenzie and MacKenzie, Astwood and others² Richter and Ellisby and Kennedy observed that certain chemical substances when given to rats, induce rapid and striking thyroid hyperplasia associated with lowered metabolic rates and other evidences of thyroid deficiency. One group of such substances is related to the aniline dyes and contains several of the commonly used sulfonamide compounds. The other group consists of substances related to thiourea. From the latter group Astwood selected thiouracil for clinical trial because it is relatively more goitrogenic and relatively less toxic than the other compounds studied.

* We wish to thank Dr Stanton M Hardy of Lederle Laboratories Incorporated, for supplying us with the thiouracil used in our studies.

In contrast to the actions of other goitrogens, such as cabbage, acetonitrile and soy bean meal, these new goitrogens produce thyroid hyperplasia even when iodine is given, although thyroline or desiccated thyroid abolishes their effect. The intense thyroid hyperplasia which they produce can also be prevented by hypophysectomy.

Rawson, Tannheimer and Peacock¹⁶ and Larson and others,¹² using radioactive iodine, found that thiouracil greatly reduces but does not abolish the capacity of the thyroid to collect iodine. This effect is maximal within an hour after the administration of thiouracil, whereas histologic changes in the thyroid are not apparent until twenty-four hours have passed. In vivo and in vitro studies by Franklin, Lerner and Chaikoff showed that thiouracil prevents the elaboration of diiodotyrosine or of thyroxine by the thyroid. It appeared that the failure of synthesis of diiodotyrosine and thyroxine accounts for the impaired capacity of the thyroid treated with thiouracil to collect injected iodine. The small proportion of iodine which always enters the thyroid despite the presence of thiouracil remains in the form of inorganic iodide.

On the basis of such studies, it has been postulated that thiouracil and analogous compounds exert their action by interfering with the production of thyroid hormone by the thyroid gland, that the resulting deficiency of thyroid hormone directly or indirectly stimulates the anterior lobe of the pituitary and that the increased secretion of thyroid stimulating hormone by the anterior lobe induces thyroid hyperplasia.

Rawson and his associates¹⁷ have shown that the effect of thiouracil on the human thyroid in cases of exophthalmic goiter is in nearly all respects identical with that observed in animals. The capacity of the human thyroid to collect iodine is promptly and markedly retarded by thiouracil. Comparison of specimens obtained from toxic thyroids before and after thiouracil therapy showed, despite the favorable clinical course induced by the drug, a measurable increase in the degree of thyroid hypertrophy which was present. The addition of iodine to thiouracil was followed by a reduction of the degree of hypertrophy which was present, despite the fact that administration of iodine under these circumstances was not followed by any increase of the iodine content of the thyroid.*

Williams and his associates²² have investigated the absorption,

* These and other observations by Rawson and his associates¹⁸ at the Massachusetts General Hospital have led them to suggest that iodine exerts two actions on the thyroid gland in cases of exophthalmic goiter: an iodinating action and an involuting action, and that these two actions can be separated one from another by means of thiouracil.

distribution and excretion of thiouracil They found it to be rapidly absorbed from the gastro-intestinal tract and readily excreted in the urine. Larger concentrations were observed in cells than in extra cellular fluid, particularly large amounts occurring in white blood cells Bone marrow, ovaries thyroid and pituitary also contained large amounts Rapid destruction of thiouracil appeared to occur in the stomach and bowel

Bielschowsky found that giving thiouracil and 2-acetaminofluorine (a potent carcinogen) to rats produced adenomatous and anaplastic, invasive tumors of the thyroid, whereas either substance alone would not do so Broders and Parkhill have called attention to the numerous mitoses and the extreme hyperplasia seen in thyroids of persons who had exophthalmic goiter which had been treated with thiouracil These observations led Hinton and Lord to suggest that, in some instances, thiouracil might prove capable of increasing the incidence of malignant lesions in the thyroid. On this basis these authors advised against its use in all cases of nodular goiter This conclusion is based entirely on theoretical considerations and, it must be emphasized, has not thus far found any support in reported clinical observations

CLINICAL CONSIDERATIONS

Since Astwood's report¹ in May, 1943 of control of hyperthyroidism by thiouracil in three cases, many reports on its clinical use have appeared. The effectiveness of the drug in controlling hyperthyroidism in practically all cases is now unquestioned, and Van Winkle and others reported therapeutic failure regardless of dose in only 4.3 per cent of cases when one excludes those failures dependent on toxic reactions

Early in its use dosages of thiouracil of 0.2 gm three times a day or more, were frequently employed. It soon became apparent that smaller doses of the drug were effective At present, in most instances 0.2 gm is given twice daily usually at 8 A.M. and at 8 P.M. Because of the rapidity with which the drug is excreted from the body it has been found more effective to give the drug in divided doses at approximately equal intervals After the signs and symptoms of hyperthyroidism have been completely controlled, smaller doses will frequently maintain a normal metabolic rate The effective maintenance dose varies and must be determined for each patient.

The time before the response to thiouracil becomes apparent has varied considerably Some observers report an apparent improvement in the patient's clinical condition after a few days of treatment but in most instances one or two weeks of treatment have

elapsed before benefit is noted Pretreatment with iodine delays the response to thiouracil and patients who have large nodular goiters respond more slowly than those who have small diffuse goiters. Many observers expect the basal metabolic rate to have become normal after about six or eight weeks of treatment However, failure to achieve this does not indicate failure of the drug, for several patients have reached normal metabolic levels only after months of treatment In our personal experience the time of treatment needed to control hyperthyroidism has been longer than in many of the reported cases It is probable that the longer time needed by patients having large nodular goiters or by those patients who have recently received iodine is due to the longer time needed to allow the exhaustion of large amounts of colloid and thyroid hormone present in the thyroid gland.

Various changes have been found to occur in the thyroid gland during treatment with thiouracil, as noted previously The gland has been reported by some observers to increase in size, while others have not noted any change in size Most observers agree that the gland becomes softer and the development of bruits over the gland is frequent The signs and symptoms of hyperthyroidism subside gradually and continuously Simultaneously the basal metabolic rate falls and the blood cholesterol increases In patients who have auricular fibrillation the cardiac rhythm may become normal, in some, however, auricular fibrillation remains as a permanent result of hyperthyroidism

The appearance of the eyes usually improves This improvement is, we believe, due chiefly to lessening of lid lag and of contraction of facial muscles, and possibly to other unrecognized factors That it is not due to lessening of protrusion of the eyeballs has been confirmed by Barr and Shorr, who found by actual measurements of the position of the globes that many patients taking thiouracil showed an increasing prominence of the eyes In their cases 2 mm. of protrusion was occasionally reached and in one instance 4 mm occurred Williams and Bissell²¹ reported one instance of serious exophthalmos developing during treatment with thiouracil Dobyns and Haines found a measurable increase in protrusion of the eyes in all of eleven patients treated with thiouracil In one instance severe exophthalmos developed In this case the progress of the protrusion of the eyes stopped when administration of thiouracil was discontinued

If administration is continued in sufficient dosage, thiouracil occasionally leads to the development of myxedema Reduction of the dose of thiouracil as soon as the signs of hyperthyroidism disappear usually, but not always, prevents such an occurrence Barr and

Shorr stated that the clinical signs of myxedema and an elevation of the concentration of cholesterol in the blood may occur before the basal metabolic rate falls below normal levels. Our experience corroborates this observation.

Thiouracil has not been used long enough to know what incidence of recurrence may follow when it is used as the total treatment of hyperthyroidism. Barr and Shorr reported that after treatment for two to seven months eleven relapses occurred in forty seven cases in which the drug had been withdrawn for from one to sixteen and a half months. Van Winkle and others reported relapses in 33.7 per cent of 1,236 cases in which satisfactory remission had been induced by thiouracil. The duration of treatment in these cases was not recorded. Many factors may determine whether a remission induced by thiouracil is permanent, as is also true when exophthalmic goiter is treated surgically. It seems probable that the intensity and persistence of the cause of exophthalmic goiter are relatively greater in some than in other cases. In a small series of our patients who had exophthalmic goiter which recurred following surgical resection of most of the thyroid gland, recurrences have also taken place after control of hyperthyroidism by thiouracil. This has also been observed by Barr and Shorr. A much longer time will be needed before any definite knowledge can be obtained of the incidence of recurrence or relapse after thiouracil therapy.

Many workers with this drug have not tried to use it as a total treatment of hyperthyroidism but have preferred to use it as a method of preoperative preparation. Early in the course of such programs it became apparent that the surgical difficulties of operating on patients prepared with thiouracil were greater than after preparation with iodine. In the former case the thyroid gland was vascular and friable and the control of hemorrhage was occasionally difficult. Although postoperative reactions were generally mild, in a few instances severe postoperative reactions occurred. This raises the question whether preparation with thiouracil will necessarily prevent a postoperative crisis. Although that question can not be definitely answered, it seems safer to administer iodine after thiouracil has controlled hyperthyroidism and before surgical treatment is undertaken. The work of Rawson and others noted previously confirms the rationale of this procedure by demonstrating involution of the thyroid as the result of administration of iodine even though thiouracil is being given. Administration of iodine also overcomes the increased bleeding and friability which cause surgical difficulties. Iodine may be given for a week or two before operation during which time administration of thiouracil may be either stopped or continued. In either case the thyroid gland becomes

noticeably firmer during the course of treatment with iodine. In some such instances the bruits do not disappear. We agree with Bartels and others who feel that iodine should always be given after thiouracil preparation of patients who have hyperthyroidism.

The most serious obstacle to the use of thiouracil is the occurrence of toxic reactions. Of these, agranulocytosis is the one of greatest seriousness. In several cases this condition has been reported to have developed and a few deaths have been recorded. Evidence presented by Moore and also by Van Winkle and his associates indicates that the occurrence of agranulocytosis is not influenced by the size of the dose of thiouracil. Moore in a study of 1,091 patients treated by twelve groups of observers found an incidence of agranulocytosis of 1.8 per cent with a death rate of 26 per cent among patients who had agranulocytosis. Van Winkle and associates reviewed 5,745 patients treated by 328 clinical investigators and found that granulocytopenia occurred in 2.5 per cent of cases, and that 14 per cent of patients who had granulocytopenia died, thus giving a total mortality rate for all the patients treated with thiouracil of 0.4 per cent.

Milder degrees of leukopenia occur frequently. They are often very transient and do not necessarily indicate interruption of treatment. When leukopenia of any degree occurs it is important that frequent leukocyte counts be made in order that treatment may be stopped before agranulocytosis occurs. Even moderate reductions of the total leukocyte count should arouse enough suspicion to call for differential leukocyte counts. Our patient who had agranulocytosis following thiouracil therapy had an absence of granulocytes in the blood smear at a time when the total leukocyte count was 4,200 in each cubic millimeter of blood. Van Winkle and his associates did not find evidence that the administration of pyridoxine, pantothenic acid, folic acid or vitamins during the time of treatment with thiouracil would prevent leukopenia and agranulocytosis.

When agranulocytosis occurs during the course of thiouracil treatment, administration of the drug should be discontinued and not started again for that patient. It has seemed a wise precaution to administer penicillin in massive doses in order to prevent, if possible, the progress or development of infections. It is beyond the scope of this paper to discuss the relative merits of different types of treatment of agranulocytosis.

Probably related to agranulocytosis as a complication is thrombocytopenia, one case of which was reported by Evans and Flink and one by Barr and Shorr. The former authors also reported two cases in which increased bleeding tendency with positive cuff test developed during treatment with thiouracil. Van Winkle stated that

purpura was reported by six of the investigators who contributed to his study

Fever is probably the commonest manifestation of toxic reaction to thiouracil. In some instances it may be so severe as to indicate withdrawal of the drug, but occasionally if the febrile reaction is not severe, administration of the drug can be stopped temporarily and reinstituted in smaller dosage without recurrence of the fever. McArthur, Rawson and Means expressed the belief that the febrile reaction is a manifestation of true drug idiosyncrasy.

Cutaneous reactions are also seen occasionally. If the rash is proved to be due to thiouracil, administration of the drug probably should be permanently discontinued. Jaundice, nausea and vomiting, muscular pains, general malaise and many other reactions have been attributed to thiouracil in rare cases. Their infrequency or their mildness make them of much less importance than agranulocytosis.

The incidence of toxic reactions and the severity of some of them make caution during the period of administration of thiouracil imperative. The patient should be under frequent observations; temperature recordings should be made frequently and leukocyte counts should be made at short intervals. Even slight reduction of leukocyte counts should be taken seriously and followed closely with differential blood counts. Since agranulocytosis may appear very abruptly, serial total leukocyte counts do not constitute adequate protection. The patient must be instructed to consult the physician at the first sign of sore throat or other evidence of infection. The dose of the drug should be reduced as soon as the evidences of hyperthyroidism have been controlled.

Moore found that reactions necessitating cessation of the drug occurred in approximately 8 to 10 per cent of the patients treated. The mortality rate in his study attributable directly to the drug was 0.5 per cent. Van Winkle and associates found that in approximately 13 per cent of cases there was some untoward reaction to thiouracil therapy. The mortality rate attributable to thiouracil in this series was 0.4 per cent, all of the deaths being due to granulocytopenia.

In view of the definite though slight risk involved in treating hyperthyroid patients with thiouracil, consideration must be given in each instance to the relative risk for that patient of the various methods of treatment available. Thiouracil has been used for too short a time for one to know definitely how frequently patients who have mild or moderately severe exophthalmic goiter may have the disease brought permanently and completely under control with the drug alone. Proper evaluation of the ultimate role that thiouracil

is to play as a total treatment of hyperthyroidism will depend on accurate comparison between the risk of toxic reactions to thiouracil and relapses following its use on the one hand, and the surgical mortality rate of subtotal thyroidectomy, the risk of parathyroid insufficiency, injuries to the recurrent nerve, and so forth, and the incidence of recurrence or persistence of hyperthyroidism following surgical treatment on the other hand.

Occasionally, patients who have hyperthyroidism are seen with complicating conditions which in themselves add materially to the risk of surgical treatment. In such cases thiouracil may be used as total treatment of the hyperthyroidism with strikingly good results. Actually in some instances in which such a program has been begun, the patient's condition has improved so greatly that operation on the thyroid has been performed later without excessive risk. Notable among such instances are patients having hyperthyroidism and severe angina pectoris in whom the cardiac condition may show great improvement after a period of control of hyperthyroidism.

The risk of partial thyroidectomy after preparation with iodine in cases of mildly or moderately severe exophthalmic goiter without complications approximates closely the risk of thyroidectomy for adenomatous goiter without hyperthyroidism. Therefore there seems, at present, to be no indication for the use of thiouracil as preoperative treatment in such cases, for the risk of administration of the drug would be added to the minimal risk of this operation. When, however, the risk of thyroidectomy is greatly increased by the intensity of hyperthyroidism, administration of thiouracil as a preoperative measure should be considered. Included in this group are, for example, patients who have extreme degrees of hyperthyroidism and large friable thyroid glands in whom anticipated technical difficulties superimposed on the severe hyperthyroidism may indicate the performance of two partial lobectomies at different times. In such cases complete control of hyperthyroidism by thiouracil may bring the patient into such condition that a double resection of the thyroid may safely be done at a single operation. In our experience such cases constitute only a small percentage of cases of exophthalmic goiter. Patients having severe hyperthyroidism associated with adenomatous goiter may show little or no improvement after administration of iodine. In such cases preparation with thiouracil, even though much time may be needed for it, can be of great help in reducing surgical risk.

It is our feeling at the present time that the most important indications for the use of thiouracil are (1) as a total treatment for hyperthyroidism in those cases in which complications prohibit surgical treatment of the disease, (2) as a preoperative treatment

in those cases in which the severity of hyperthyroidism is responsible for an anticipated high surgical risk or (3) as a preoperative treatment in those cases in which complications increase the surgical risk, especially if temporary relief of hyperthyroidism will bring about some amelioration of the complicating condition. It is not our practice to use the drug as a preoperative treatment of patients who have mild or moderately severe exophthalmic goiter for the time involved is long and, in our opinion, the ultimate risk to the patient will not be lessened. Also, we have not used thiouracil as total treatment for hyperthyroidism in cases of mild or moderately severe exophthalmic goiter, for we felt that the drug could not be administered without constant careful observation. We feel that the risk of administration of the drug in such cases is as great as, or greater than the risk of partial thyroidectomy in similar cases.

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THE CLINICAL ADMINISTRATION OF STREPTOMYCIN

H CORWIN HINSHAW AND WALLACE E HERRELL

STREPTOMYCIN is an antibiotic substance which was announced in January 1944, by Schatz, Bugie and Waksman. During the two years which have elapsed since this announcement, a large amount of pharmacologic, bacteriologic, experimental and clinical information has been collected concerning streptomycin. Streptomycin is of sufficiently low toxicity and has sufficiently effective antibacterial properties to give rise to the belief that it will become a useful chemotherapeutic preparation for the treatment of some important human diseases. In view of the probability that streptomycin will soon be available commercially and the fact that it possesses some peculiar properties which must be understood if it is to be used effectively, an effort will be made in this publication to summarize that information which may be of interest and value to the clinician.

Streptomycin is derived from cultures of an actinomycete of the soil (*Streptomyces griseus*) by a process of extraction and purification which yields a highly soluble hygroscopic powder usually cream-colored or light tan in appearance. Streptomycin is a basic substance and is prepared at the present time either in the form of streptomycin hydrochloride or streptomycin sulfate. Although streptomycin is considerably more stable than is penicillin it is recommended that the material be refrigerated, especially when in solution, and that solutions be freshly prepared. In earlier publications the unit of potency was defined on the basis of its antibacterial properties but in recent months this designation has been discontinued and the metric system has been substituted. One microgram of pure streptomycin base is approximately equivalent to the original "S" unit of Waksman; hence 1 mg. of streptomycin is approximately equal to 1,000 "S" units and 1 gm. of streptomycin is equivalent to 1,000,000 "S" units.

DOSAGE AND ADMINISTRATION

Streptomycin is usually administered by the intramuscular route and solutions containing 100 to 250 mg. per cubic centimeter are usually preferred. Some more highly purified preparations are well tolerated subcutaneously in similar concentrations but other preparations contain irritant impurities which make this route less desirable than the intramuscular route. Streptomycin may be given intravenously but concentrated solutions should not be ad-

by this route because of the occasional presence of physiologically potent impurities which might produce disastrous results. Streptomycin may be given in very dilute solution by continuous intravenous infusion, the daily dose being dissolved in 1 or 2 liters of isotonic saline solution or 5 per cent solution of glucose. The addition of 100 mg of heparin to each liter of solution of streptomycin intended for intravenous infusion will minimize the possibility of venous thrombosis.

At the present time the minimal daily dose of streptomycin appears to be 1 to 2 gm (1,000,000 to 2,000,000 "S" units) for most of the infectious diseases for which streptomycin is recommended. The drug is excreted less rapidly than in the case of penicillin but when given by the intramuscular or subcutaneous route it is advisable that the doses be administered every three to four hours, or at most at intervals of six hours. It has been our practice in recent months to inject intramuscularly or subcutaneously 2 or 3 c.c. of a solution containing 100 mg per cubic centimeter every four hours, making a total dose of 1.2 to 1.8 gm for each twenty-four hours.

Streptomycin is excreted by the kidneys for the main part and from 60 to 80 per cent of the amount injected may be recovered in the urine. It is also excreted in the bile in a concentration somewhat higher than that of the blood serum. When doses recommended previously are employed the concentration of streptomycin in blood serum rises rapidly following the injection to a level of 15 to 25 micrograms per cubic centimeter of blood serum and falls to a low level of 3 to 8 micrograms four hours later. These levels should be theoretically adequate to inhibit the growth of most pathogenic micro-organisms which are regarded as sensitive to this drug. Streptomycin is more active in a slightly alkaline or neutral medium than it is in an acid medium. Hence it is preferable to alkalinize the urine when it is desired that this fluid possess maximal antibacterial properties. It should also be remembered that pus is likely to be acid in reaction, a fact which may limit the effectiveness of streptomycin in purulent exudates.

When administered by mouth streptomycin is found to possess some characteristics which are unique among known antibiotic substances. Streptomycin is not absorbed from the gastro-intestinal tract to any appreciable degree, no significant amount appearing in the blood or urine. The drug is not destroyed in the lumen of the bowel but there it remains and can be recovered in the feces. Streptomycin exerts an antibacterial effect on the intestinal flora, reducing the total bacterial count but acting more intensely on the colon bacillus and allied organisms than on other bacteria.

CLINICAL USES

The antibacterial action of streptomycin is sufficiently restricted to make it appear urgent that the drug should be used only when there is bacteriologic proof of the nature of the infecting organism. Whenever possible, tests should be carried out to determine the sensitivity of the organism to the action of streptomycin *in vitro* especially in those instances in which this property is known to be widely variable within the species.

It is important to emphasize strongly that streptomycin is in no sense a substitute for penicillin. Penicillin is active against many bacteria, most of which react positively to Gram's stain. Streptomycin has the fortunate property of being effective against many organisms of the gram negative type, especially those of bacillary form, but there are exceptions to this generalization. It is immediately obvious that the clinician is destined to become more and more dependent on the clinical bacteriologist for guidance in his selection of therapeutic substances in treatment of infectious disease.

Unfortunately, many micro-organisms which are initially quite sensitive to the action of streptomycin rapidly acquire a degree of drug fastness which may prevent the successful application of this remedy. In the case of some organisms of the *coli aerogenes* group drug fastness may develop within a few days of treatment. The therapeutic implications of this fact are obvious and require that the drug be given in large doses and without interruption during initial phases of the therapeutic program. It is suggested that in most instances treatment should not be undertaken unless an adequate supply of streptomycin is on hand to permit a thorough course of treatment without interruption since interruption might permit the organism to acquire resistance to the action of streptomycin. Resistance is much more likely to occur in chronic infections or under those circumstances in which reinfection is prone to occur than under other circumstances.

Among the diseases which have proved to be amenable to streptomycin therapy *tularemia* appears to respond in the most dramatic manner. Foshay and Pasternack have described seven cases in which tularemia has responded promptly and most dramatically to streptomycin administered in doses considerably less than the doses which have appeared to be required for other diseases. It appears from this report that streptomycin is an unqualified success in the treatment of tularemia and this fact will make the accurate diagnosis of this disease even more important than it has been previously.

Streptomycin has been found to be effective in the treatment of *bactericemias* when the infecting organism is one which is susceptible.

to the action of this drug.⁶ This is especially true of the bacteremias due to gram-negative bacilli, including those which occur occasionally following severe infections of the genito-urinary tract.

Streptomycin is of value in the treatment of some infections of the urinary tract which may be resistant to the action of sulfonamides and penicillin.^{5, 6} There is a striking tendency to recurrence of such infections of the genito-urinary tract and a tendency of residual organisms to develop marked resistance to the effect of streptomycin. For this reason every effort should be made to assure adequate drainage of the urinary tract prior to institution of streptomycin therapy; efforts should be made to dispose of indwelling catheters or to close suprapubic cystotomy incisions or nephrostomy incisions, if this can possibly be achieved before streptomycin treatment is instituted. Streptomycin should be given in doses of 1 to 2 gm or more per day and if a successful therapeutic result is not realized within a few days it may be assumed that streptomycin-sensitive organisms are no longer present. In the case of neurogenic bladders with retention it is important that, before streptomycin treatment is started, residual urine be reduced to a minimum and an automatic bladder be established which does not require catheterization.

Streptomycin has been used in treatment of *typhoid fever*.^{8, 10} with results which were described as uncertain but suggesting therapeutic effect. Further studies should be carried out employing larger doses given simultaneously by both the oral and the parenteral route of administration. In view of the great prevalence of typhoid infection in many sections of the earth and the lack of any other chemotherapeutic remedy, it is immediately obvious that this subject deserves more investigation when supplies of the drug permit.

Infections of the respiratory tract are occasionally due to organisms which are sensitive to the action of streptomycin and some success has been realized^{6, 9} in treatment of chronic infections due to bacteria belonging to the genera *Klebsiella* and *Hemophilus*. Waksman and Schatz have reported that *Hemophilus pertussis* was found by F. R. Heilman to be highly sensitive to the action in vitro of streptomycin. Likewise, studies in vivo by Bradford and Day and by Hegarty, Thiele and Verwey have shown a protective effect of streptomycin in experimental pertussis. Our colleague, A. M. Olsen, has utilized streptomycin by nebulization against some residual organisms present in the tracheobronchial tree in cases of bronchiectasis in which the patients have been treated previously with penicillin aerosol.⁹ It has also been noted that *ozena* due to a susceptible strain of *Klebsiella* has shown some temporary improve-

and in which the patient appears to be responding to streptomycin therapy

Our colleagues in the Section on Pathologic Anatomy have performed necropsy in five cases in which prolonged streptomycin therapy had been administered in the doses recommended elsewhere in this paper and with the material available to us. In none of these instances have lesions which could be attributed to toxicity of streptomycin been observed in the kidneys, the liver, the central nervous system or other organs. Streptomycin has not shown toxic potentialities to the hematopoietic system or the gastro-intestinal tract nor have disturbances of renal or hepatic function been observed despite extensive studies in search for such toxic properties.

SUMMARY

Streptomycin is a drug of low toxicity for man and has antibacterial properties in vitro and in vivo against a number of pathogenic micro-organisms which are not susceptible to other chemotherapeutic preparations.

Suggestions are made as to dosage, routes of administration and continuity of administration. The most important limiting factor in therapy seems to be the ability of many sensitive micro-organisms to develop a resistance to the antibacterial effects of streptomycin.

Eventually, streptomycin will undoubtedly be available commercially but in the meantime production is under way on a limited scale. The available supply of the material is being used largely for investigational work. During this experimental period, cases should be selected with great care and all possible information should be collected which will serve as a guide for final evaluation of the therapeutic possibilities of streptomycin.

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purulent secretions and prevention of hemoptysis and of episodes of fever caused by retention of secretions. Treatment can best be considered in three phases: first, measures to improve general health and nutrition of the patient; second, medicinal, postural and mechanical aids in elimination of secretions; and third, use of vaccines, drugs and antibiotic agents to combat bacterial infection in the bronchial tree. Surgical procedures, such as artificial pneumothorax and phrenic neurectomy, long since have been abandoned in treatment of bronchiectasis.

GENERAL MEASURES IN TREATMENT OF BRONCHIECTASIS

As in any other chronic infection, measures must be taken to improve the patient's general condition. Adequate rest, good food and good environment are always helpful. Sunlight and ultraviolet light should be beneficial. Upper respiratory infections should be avoided at all costs and when colds occur they should be treated promptly. A warm, dry climate is advantageous because the patient is less likely to have upper respiratory infections. On the other hand, a cold, moist, changeable climate makes control of bronchiectasis more difficult. Inhalation of dust, fumes and smoke is undesirable for the patient who has bronchiectasis and he is wise not to smoke.

MEASURES HELPFUL IN ELIMINATING BRONCHIAL SECRETIONS

In all suppurative disease it is essential that pus be drained. External drainage with rib resection is rarely justifiable in bronchiectasis. Hence drainage of dilated bronchi and bronchiectatic abscess must take place by the bronchial and oral route. The pulmonary secretions are often thick and viscid and the patient frequently experiences great difficulty in dislodging these secretions from the smaller bronchi. Expectorant drugs, such as the iodides, creosote and ammonium chloride, are helpful in thinning out secretions so that the patient can cough them up with less effort. Steam inhalations also may be beneficial.

Since most of the dilated bronchi are in the lower lobes, normal posture is a deterrent to proper bronchial drainage. Gravity can be used to advantage in emptying the bronchial tree if the patient will invert himself so that the head is down and the hips are higher than the shoulders. This position can be assumed over the edge of the bed or over a chair so that secretions will tend to flow out through the trachea and mouth. Postural drainage should be repeated at least four times daily before each meal and at bedtime for ten to twenty minutes each time. A modified form of postural drainage consists of elevating the foot of the patient's bed 12 to 18 inches (30 to 46 cm). Some patients discover certain positions which are

particularly effective in getting rid of secretions. The best position for postural drainage is often dictated by the location of the bronchiectasis and the experience of the individual patient.

Bronchoscopy should be performed at least once in every case of bronchiectasis. Bronchial obstructions, such as foreign bodies, tumors, broncholiths or bronchostenosis, may be discovered. The relief of any bronchial obstruction will be helpful. In some cases repeated bronchoscopic aspirations may be beneficial. In the absence of bronchial obstruction a great many patients can eliminate pulmonary secretions by carrying out a program of adequate postural drainage. In our experience the irrigation of the bronchial tree with various solutions is seldom indicated. Undoubtedly bronchoscopic treatment has merit in certain cases but routine use of the bronchoscope in treatment of bronchiectasis is not advocated.

The frequent instillation of iodized oil by the supraglottic or catheter method has been recommended by some authorities. Theoretically, oil displaces pus in dilated bronchi and hence it is easier for the patient to raise secretions. In experience at the Clinic only occasionally does a patient feel that he benefits by treatment with iodized oil.

Watson and Kibler stated the opinion that allergy plays a major part in the etiology of bronchiectasis. They have emphasized the importance of treating the allergic manifestations of the disease. Thomas, Van Ordstrand and Tomlinson reported that half of 190 patients examined by them had major allergy. At the Clinic, our impression is that asthma and other diseases due to allergy are not primary factors in the etiology of most of our cases of bronchiectasis. In many cases of asthma in which the presence of bronchiectasis is suspected, bronchographic studies fail to reveal significant bronchial dilatation. In a few instances diffuse cylindrical dilatation of the bronchi is seen in the lower lobes. The bronchographic picture of bronchiectasis complicating asthma is usually strikingly different from the saccular and cylindrical type of bronchial dilatation commonly seen in cases in which allergy is not present. The so-called allergic type of bronchiectasis is seldom amenable to surgical treatment. When asthmatic bronchitis and bronchiectasis are associated, treatment of the allergy is indicated. Thomas and his associates report good results in treatment of allergy by hyposensitization, dietary restrictions and autogenous vaccines. Also they advised patients to avoid contact with known allergens.

TREATMENT OF SECONDARY BRONCHIAL INFECTION

When bronchiectasis is present, bronchial secretions usually contain many different types of bacteria. On examination of smears of

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When bronchiectasis is present, bronchial secretions usually contain many different types of bacteria. On examination of smears of

the sputum a mixed flora is seen and it is difficult to make cultures which demonstrate predominant organisms. All kinds of gram-positive and gram-negative bacteria are present and fusiform bacilli, spirochetes and yeasts are recognized often. Both pathogenic and nonpathogenic organisms occur in abundance. Thus attempts to make vaccines from the sputum of patients who have bronchiectasis are not successful. Arsenicals are of value only for treatment of spirochetal infections.

Sulfonamide Compounds—When sulfonamide drugs were discovered, it was hoped that they would prove to be valuable in treatment of chronic, suppurative, pulmonary disease. Experience has shown that their value in bronchiectasis is limited. This is perhaps due to the multiplicity of the bacteria found in the pulmonary secretions, as well as to the difficulty in getting the drug to the organisms themselves. However, Norris has reported that sulfonamide drugs administered orally can be recovered from pulmonary secretions. At the Clinic we have used sulfonamide drugs in the preoperative preparation of patients who were to undergo pulmonary resection for bronchiectasis. The drugs have been used in association with other measures, such as postural drainage and expectorant medicaments, and we have felt that they were helpful in prevention of postoperative complications. In nonsurgical bronchiectasis results have been less gratifying. Oatway has reported that partial relief of bronchorrhea was obtained in a series of sixteen patients treated with sulfonamides. The improvement was usually temporary and subsequent courses of sulfonamides were necessary to maintain improvement. Thomas, Van Ordstrand and Tomlinson felt that chemotherapy was most valuable when used in combination with treatment* of allergy, postural drainage and administration of iodides.

Antibiotic Agents—Penicillin administered parenterally has been of somewhat greater value than sulfonamides in treatment of bronchial infection. White and his associates have stated that penicillin given by intramuscular injection is useful in preoperative and postoperative management of patients undergoing pulmonary resection. Postoperative empyema and other complications were reduced greatly. In some cases of chronic nonsurgical bronchiectasis patients reported that the volume of sputum was reduced when they were taking penicillin but many reported that penicillin was ineffective. Benefits obtained are likely to be temporary.

When adequate supplies of streptomycin become available, penicillin combined with streptomycin may prove to be effective in overcoming much of the infection that is present in chronic bronchiectasis. However, any method of chemotherapy or treat-

ment with antibiotics should be used as an adjunct to the general measures already outlined

Nebulization—Inhalation of nebulized solutions of antibiotic preparations is being given thorough trial. Preliminary reports concerning our experience with the method have been presented^{5 10 11} and further reports will be made when a sufficient number of patients have been treated. Nebulization of solutions of sulfonamides has been carried out by Castex, Capdehourat and Lavarello and a number of other investigators. Methods of nebulizing penicillin have been worked out by Bryson, Sansome and Laskin. Mutch and Rewell, Hagens, Karp and Farmer and others. Barach and his associates have presented their preliminary results.

A description of methods of administering nebulized solutions is beyond the scope of this paper. However, it should be emphasized that prolonged daily periods of nebulization are advisable. At the present time penicillin in concentrations of 10,000 units per cubic centimeter is recommended at the Clinic and the patients are using 20 to 30 c.c. of the solution during each day. Whenever streptomycin has been available, 500,000 S units (0.5 gm.) has been mixed with 200,000 Oxford units of penicillin in 20 to 30 c.c. of physiologic saline solution. Our patients have been hospitalized for aerosol treatment because oxygen has been used as a source of positive pressure. Accurate charts of the amount, character and odor of the sputum have been kept.

In our experience treatment with penicillin aerosol has produced a striking reduction in the amount of sputum in about half of the cases. The reduction of the volume of sputum demonstrated in these patients was at least 75 per cent or more. Bacteriologic studies have shown that the organisms were predominantly gram positive. In patients whose response to penicillin was less satisfactory the bacterial flora of the sputum contained gram negative organisms.

A limited supply of streptomycin has been made available through the courtesy of Dr. D. F. Robertson of Merck and Company and has been administered with the co-operation of Dr. H. C. Hinshaw. We have had an opportunity of using streptomycin aerosol in a number of cases and have combined it with penicillin. The results of aerosol treatment of bronchiectasis with combined penicillin and streptomycin have been satisfactory. The daily volume of sputum has been greatly reduced and smears and cultures have revealed that the bacteria have been eradicated.

Both penicillin and streptomycin may be instilled directly into the bronchial tree. The method is similar to that employed in the instillation of iodized oil for bronchography. A number of patients with bronchiectasis have been treated in this way and it is felt that

intratracheal treatment may prove to be a valuable adjunct to nebulization

Nebulization treatment appears to be of considerable value in preparation of patients with bronchiectasis for pulmonary resection. Relief of bronchorrhea in most patients with nonsurgical bronchiectasis may be obtained when nebulization is used in combination with postural drainage, bronchoscopic aspiration and other accepted methods of therapy. Although the patient's improvement may be temporary, it is probable that he can control his symptoms by further nebulization on a modified scale.

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THE THIOCYANATES IN THE TREATMENT OF HYPERTENSIVE DISEASE

EDGAR A. HINES JR.

THE thiocyanates have been in and out of favor for treatment of hypertension since Pauli first advised their use in 1903. In 1936, Barker introduced a satisfactory method of preventing overdosage. He suggested that the dosage of the drug be controlled by frequent determinations of the concentration of thiocyanate in the blood. Since then this type of treatment for hypertension has been used widely but not always properly or safely. The purpose of this presentation is to discuss in some detail by the question and answer method the present concept of the mode of action, methods of proper administration and possible results of the use of thiocyanates in treatment of hypertensive disease.

ACTION OF THIOCYANATES

What is the Pharmacologic Action of Thiocyanates?—The pharmacologic action of the thiocyanates has not been investigated extensively and the way in which these drugs act to lower blood pressure or to relieve symptoms has not been explained satisfactorily. There seems little doubt that, even in nontoxic amounts, these drugs have a depressant action on the central nervous system. Clinically this is corroborated by the drowsiness and lassitude which many patients notice especially during the early days of a period of treatment and satisfactory results reported by some physicians from the use of these drugs in treating severe insomnia. The thiocyanates are known to relax smooth muscle tissue but there is no proof that this results in significant dilatation of small arteries or arterioles in man. In my experience large single doses (3 to 5 gm) of the sodium salt of thiocyanate does not produce significant vasodilatation of the vessels of the skin of patients with essential hypertension. Two other known effects are local reduction of tissue oxidation and through its action on the thyroid gland, reduction of the basal metabolic rate.

Do the Thiocyanates Lower Blood Pressure?—No evidence has been found that the thiocyanates affect blood pressure in normal animals except when they are given in severely toxic amounts. The effect of this drug on the blood pressure of patients with hypertension still is not settled to the satisfaction of all investigators of this prob-

lem However, numerous clinical reports,¹⁻⁵ in some of which the studies were fairly well controlled, indicate that the blood pressure is lowered significantly (from 20 to 60 mm systolic and from 10 to 30 mm diastolic) in from a third to a half of patients suffering from various types and degrees of hypertensive disease In my experience with hypertension, groups 1 and 2 (Keith-Wagener classification) about half of the patients who had labile blood pressure had significant lowering of blood pressure as long as an adequate concentration of thiocyanate was maintained in the blood The majority of patients who had hypertension, groups 3 and 4, and those who had hypertension and high fixed ranges of blood pressure, group 2, have not experienced much lowering of blood pressure unless the concentration of thiocyanate in the blood was maintained at levels near the upper limits of safety (around 15 mg per 100 cc) However, in a small group of patients whose blood pressures were carefully checked the range was from 250 to 300 mm systolic and from 140 to 160 mm diastolic The blood pressures decreased 100 mm or more systolic and 50 mm or more diastolic while the patients were being treated with thiocyanate

It is to be hoped that further carefully controlled studies of blood pressure will be carried out so that the effect of the thiocyanates on the blood pressure of patients suffering from various degrees and types of hypertensive disease will be better understood

Do the Thiocyanates Relieve Symptoms Due to, or Related to, Hypertensive Disease?—Almost all investigators who have studied the effects of thiocyanates on hypertension agree that the majority of patients who have no marked unpleasant toxic effects from the drug, experience complete disappearance or considerable lessening of symptoms, such as headache, vertigo and nervous tension The relief experienced from taking thiocyanates may be due to their sedative effect but this is not an adequate explanation of their action for relief has resulted which had not been obtained previously from the use of sedatives In dealing with symptoms which are as hard to evaluate as headache and vertigo it is difficult to determine whether the relief experienced results from psychotherapy or specifically from administration of the drug Several observers have noted a return of symptoms when administration of thiocyanates was stopped and placebos were given Subsequent relief of symptoms occurred when treatment with thiocyanates was resumed However, a well-controlled study on a large group of patients has not been reported as yet

Migraine, which frequently is associated with hypertensive disease, especially among women, is relieved greatly by treatment with thiocyanates Often these headaches, as well as the so-called

hypertension headaches, are relieved completely even when blood pressure is not lowered markedly. In my opinion and in the opinion of Page and Corcoran, relief from severe headache not helped by other measures alone may justify the use of thiocyanates in the treatment of hypertensive disease in selected cases.

TREATMENT WITH THIOCYANATES

How is the Administration of Thiocyanates Controlled?—The dosage of thiocyanates for the individual patient may be controlled easily and accurately by the periodic determination of the level of thiocyanate in the blood. This determination is not difficult and the standard method used is within the technical capabilities of any clinical laboratory in which routine determinations of the constituents of the blood such as sugar or urea, are made. Description of a satisfactory colorimetric method follows.

Solutions needed are (1) a 10 per cent solution of trichloroacetic acid (2) ferric nitrate reagent, (3) thiocyanate stock solution and (4) standard solutions made from the stock solution.

To make the ferric nitrate reagent dissolve 50 gm. of crystallized ferric nitrate in 500 c.c. of distilled water. Add 25 c.c. of concentrated nitric acid and make up to 1 liter with distilled water.

For the thiocyanate stock solution dissolve about 1 gm. of potassium thiocyanate in 800 c.c. of distilled water. Titrate a 20 c.c. portion of a standard solution of silver nitrate (made by dissolving exactly 2.9195 gm. of silver nitrate in 1 liter of distilled water acidified with 5 c.c. of concentrated nitric acid) with the solution of potassium thiocyanate, using ferric ammonium sulfate as an indicator. Calculate the amount of water which it will be necessary to add to the solution of potassium thiocyanate to make 20 c.c. equivalent to 20 c.c. of solution of silver nitrate. Add the calculated amount of water to the solution of potassium thiocyanate, mix thoroughly and check the solution by another titration to make sure the solution of potassium thiocyanate is exactly equivalent to the solution of silver nitrate.

Make three dilutions of the thiocyanate stock solution to give the following three standards. 1 Dilute 100 c.c. of stock solution with water to make 1 liter. This gives a standard solution which contains 0.5 mg. of the thiocyanate ion in 5 c.c. of solution. 2 Dilute 70 c.c. of stock with water to make 1 liter. This gives a standard solution which contains 0.35 mg. of the thiocyanate ion in 5 c.c. of solution. 3 Dilute 40 c.c. of stock with water to make 1 liter. This gives a standard solution which contains 0.2 mg. of the thiocyanate ion in 5 c.c. of solution.

The method of performing the test is as follows Transfer 6 c.c. of the 10 per cent solution of trichloroacetic acid to a test tube Add 6 c.c. of serum or plasma Stopper and shake well Allow to stand ten to fifteen minutes Filter through a small filter paper The filtrate should be perfectly clear If it is not, filter again through the same filter paper Measure 5 c.c. of filtrate into a clean dry test tube Add 1 c.c. of the ferric nitrate reagent. Mix and read in a colorimeter with the standard solution set at 20 mm Choose that standard solution which most nearly matches the unknown The standards are made as follows Transfer 5 c.c. of each of the three standard solutions to three test tubes Add 5 c.c. of solution of trichloroacetic acid and 2 c.c. of the ferric nitrate reagent to each Mix.

With the standard solution set at 20 mm for the colorimetric comparison the calculation may be simplified to the three following forms, depending on the strength of the standard

1 When the 0.5 mg standard is used, divide 200 by reading to obtain the number of milligrams of the thiocyanate ion in 100 c.c. of serum 2 When the 0.35 mg standard is used, divide 140 by the reading to obtain the number of milligrams of the thiocyanate ion in 100 c.c. of serum 3 When the 0.2 mg standard is used, divide 80 by the reading to obtain the number of milligrams of the thiocyanate ion in 100 c.c. of serum

What Preparations of Thiocyanate May be Used and What is the Method of Administration?—Either sodium or potassium thiocyanate may be used. The potassium salt is used more often for oral administration It may be given in solution or in tablets The vehicle most often used for a solvent is simple elixir or peppermint water, most patients prefer the latter In the early days a solution was used almost exclusively, but in recent years, an enteric coated tablet has become the more favored method of administration The enteric coated preparation has the disadvantage of not always being easily dissolved in the gastro-intestinal tract and for this reason in some instances it may be more difficult to maintain a constant level of thiocyanates in the blood with this type of medication than when a solution of the drug is used The sodium salt of thiocyanate is used more often for intravenous administration A 5 per cent solution of sodium thiocyanate in sterile distilled water may be given intravenously in cases in which treatment with thiocyanate is not contraindicated and when it is certain that the patient has not taken any thiocyanate recently However, about the only situation in which the intravenous method of administration is the one of choice is that in which the patient is having a severe attack or a series of frequent attacks of severe migraine or head-

ache due to hypertension. In these cases it may be desirable to obtain a therapeutic concentration of thiocyanate in the body quickly. The same amount of the potassium salt may be used for intravenous administration but it should be diluted in 500 c.c. of sterile physiologic saline solution and administered by the slow drip method inasmuch as a high concentration of potassium may cause considerable local irritation of the vein into which such a solution is injected and may produce chemical thrombophlebitis.

What is the Dose of Thiocyanates?—The thiocyanates at first should be given in amounts so that the level of thiocyanate in the blood is maintained at between 8 and 12 mg per 100 c.c. If satisfactory results are obtained at this concentration the dosage may be decreased so that a level of 4 to 6 mg. per 100 c.c. is maintained, inasmuch as this is adequate in some cases and at the lower concentrations unpleasant side effects such as fatigue and lassitude are less noticeable. In some patients it will be found necessary to maintain the level at about 12 mg per 100 c.c. for a satisfactory effect. If no evidence of any renal insufficiency is found, the initial daily dose may be 12 grains (0.78 gm) in divided doses of 2 or 3 grains (0.13 or 0.2 gm) each. Subsequent dosage should be adjusted to maintain the desired level of thiocyanate in the blood. The maintenance dose may vary considerably for different patients from as little as 3 grains (0.2 gm) to as much as 21 grains (1.36 gm) daily. The commonest requirement is a daily dose of between 6 and 9 grains (0.4 and 0.6 gm).

It is safest to give the patient written instructions each time the dose is changed. This is advisable because among the early symptoms of intoxication is mild mental confusion and the patient in this situation may not remember the exact verbal instructions given and may "add fuel to the fire" by mistakenly taking two or three times the advised dose. I have observed this in two instances and severe toxic effects resulted from overdosage.

If it is considered advisable to give the initial dose intravenously from 2 to 5 gm (30 to 77 grains) of the sodium or potassium salt in solution may be administered. The precautions mentioned should be observed.

How Often Should the Level of Thiocyanate in the Blood be Determined?—The interval between the first and subsequent determinations of the level of thiocyanate in the blood depends on the size of the daily dose and the adequacy of the patient's renal function.

If an initial dose of as much as 12 grains (0.78 gm) daily is used, the first determination should be made not later than the seventh day and subsequently every week or ten days until the

maintenance dose of the drug has been determined. If an initial dose of 6 to 9 grams (0.4 to 0.6 gm) daily is used, the first determination should be obtained not later than the tenth day and subsequently at the same intervals as for the greater initial dosage. Even after a stable maintenance dose has been calculated, the level should be determined at least every two or three months as long as the patient takes the drug. Although for the same individual the excretion of the drug is fairly constant, the possibility is always present that at some time in the subsequent course of the disease function of the kidneys may be impaired by added vascular damage from the hypertensive disease and the rate of excretion of the drug may decrease. Therefore, it is not wise to continue administration of the drug for long periods without knowing at what level the thiocyanate is being maintained in the blood.

If definite impairment of renal function is present before the type of treatment to be used is decided on, it is usually best not to administer thiocyanates. An exception might be a patient with only slight impairment of renal function with severe headache of the migraine or hypertension type. If thiocyanates are used under such circumstances an initial dose of only 6 to 9 grams (0.4 to 0.6 gm) daily should be given and the level of thiocyanate in the blood should be determined first not later than the fourth or fifth day after starting administration of the drug and subsequently at somewhat shorter intervals of time than in the program just suggested.

What Are the Toxic or Untoward Effects Which Should be Watched For?—Mild degrees of lassitude and weakness affect many patients even when levels of thiocyanate in the blood are within the so-called safe therapeutic range. This is not an indication for discontinuing administration of the drug and in most instances it ceases or no longer is annoying after a few days or weeks. Occasionally severe degrees of exhaustion and weakness may occur. If they persist for more than a day or two, it is best to discontinue attempts to use the drug.

Maculopapular eruptions occur about a week or ten days after the beginning of treatment in about 5 per cent of cases and erythematous dermatitis in a smaller number. These eruptions clear up within a few days after discontinuing administration of the drug and do not recur on resumption of administration in about half of these patients. Consequently, unless the dermatitis is unusually severe, another trial of the drug can be begun within a week or ten days. Exfoliative dermatitis has been reported to result from the thiocyanates but this is a rare complication and as far as I know has not occurred in any of the patients treated with thiocyanates at the Clinic. Purpura occurs occasionally and if of more

than a mild degree probably warrants discontinuance of treatment with the drug. I have continued the use of thiocyanates, however in several cases in which mild purpura developed and marked benefit had been obtained from the treatment without any apparent increase in the extent of the purpura or any other untoward effect.

Although severe symptoms of toxemia have been reported when the level of thiocyanate was less than 12 mg per 100 c.c. of blood I have not observed any such symptoms which were due certainly to the thiocyanates in any of a group of more than 300 cases in which the levels were less than 15 mg per 100 c.c. The few cases which I have encountered in which severe toxic symptoms occurred were those in which the drug had not been administered properly and the concentration in the blood had reached a high level of from 20 to 50 mg per 100 c.c. I have encountered also five cases in which the concentrations had reached high levels but no toxic symptoms and no untoward effects occurred. However if the thiocyanates are to be used safely, the signs of toxicity should be recognized early and when they occur administration of the drug should be discontinued regardless of the concentration of thiocyanate in the blood.

Nausea, vomiting and marked weakness are among the significant signs of beginning severe toxic reactions. Mental disturbances commonly occur. They range from mild drowsiness and lapses of memory to signs of severe psychosis with hallucinations and disorientation. These are symptoms of a severe and sometimes fatal reaction to the thiocyanates and should not occur if the proper precautions have been taken and if the drug is discontinued when mild symptoms of toxicity appear.

Occasionally the so-called cyanate goiter may develop. Accompanying the goiter symptoms of mild or severe hypothyroidism may be observed. These symptoms are relieved when desiccated thyroid is administered in appropriate doses whether or not administration of thiocyanate is discontinued. Small doses of iodides may prevent the occurrence of the goiter but goiter is such a rare complication that it seems impractical to use iodides routinely for prevention.

At the Clinic, osteoporosis associated with moderate to severe pain has been observed in seven patients who were taking thiocyanates. The exact mechanism of the production of osteoporosis is not understood. Pain subsides and osteoporosis usually disappears when treatment with the thiocyanates is discontinued.

What Are the Contraindications to the Use of Thiocyanates?
—Contraindications are (1) moderate or severe degrees of renal

insufficiency, (2) arteriosclerosis of the central nervous system or moderate or severe degrees of organic disease of the central nervous system of any type, (3) blood dyscrasias, especially thrombocytopenic purpura, (4) somnolence or coma from any cause, (5) history of severe degrees of sensitivity to drugs, (6) inability of the patients to have determinations of the level of thiocyanate in the blood made at appropriate intervals, (7) recent or poorly healing fractures of bones or severe osteoporosis and (8) severe congestive heart failure

Thiocyanates should be given especially cautiously (1) to patients more than sixty years of age, (2) in the presence of slight degrees of renal insufficiency, (3) in the presence of mild hypertensive encephalopathy, (4) in the presence of mild congestive heart failure, (5) to patients with histories of mild or questionable sensitivity to drugs or any type of purpura, (6) to patients with mild degrees of osteoporosis or (7) to patients with any type of debilitating disease, such as tuberculosis or carcinoma

What Are the Indications For the Use of Thiocyanates?—The indications for use of thiocyanates in treatment of hypertension are not agreed on. Some clinicians advise a trial of the drug for any patient with moderate to severe degrees of hypertension who does not have some complication, such as severe renal failure or marked cerebral involvement, which might make the trial too hazardous. Others advise its use only for patients who have severe headaches due to hypertension not controlled by other measures.

The type of patient for whom the use of thiocyanates is especially indicated is the relatively young patient with labile blood pressure who has severe migraine or headaches due to hypertension. Administration of the drug to patients less than fifty years of age who have severe and progressing hypertensive disease of group 2 or 3 may be given a trial even though the patients have no significant symptoms. Patients less than sixty years of age with any group of hypertensive disease who have headaches or tinnitus and vertigo may be benefited. Patients with malignant hypertension with good renal function but with severe headaches may experience considerable relief of headache even though the blood pressure may not be lowered significantly. The thiocyanates should be used cautiously in patients more than sixty years of age and preferably only when severe symptoms are not relieved by other and simpler methods of treatment.

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THE ABUSE OF SEDATIVE DRUGS IN THE PRACTICE OF MEDICINE*

FREDERICK P MOERSCH

Few physicians would willingly surrender the privilege of intelligently employing sedative agents. Most physicians are in accord that the unwise use of sedative drugs is a practice to be condemned. I believe that these thoughts meet with the approval of most of us. Why is it then that we physicians, as the guardians of health, at times permit our patients to fall into evil ways and employ sedatives with reckless abandon?

The answer is not difficult to find. Sedative drugs which are now available are of tremendous aid to the physician and few of us would voluntarily turn back the pages of medical progress and be limited to the concoctions of our forefathers. The laity, too, has long since come to recognize the soothing effects of sedatives and all too cheerfully accepts a salty "nerve tonic" or a colored capsule which is a passport to tranquillity and oblivion.

HISTORICAL DATA

The use of sedative agents is not of recent origin but is referred to all through the pages of history. Alcohol, of course, was probably used before recorded history and opium was known to the priest physician of legendary medicine. Hippocrates¹⁶ referred to the use of mandrake (*Mandragora*) and other sedative agents. Homer¹⁸ has Helen of Troy serve a "wine of oblivion" which lulled all pain and anger and brought forgetfulness of every sorrow. It is recorded that the Arabs, the Hindus and the Greeks were well acquainted with the Jimson weed (*Datura stramonium*). And our word assassin comes down to us through the centuries from the secret tribal use of hashish (*Cannabis indica*).

Today the physician has at his disposal an almost endless array of sedative agents. Unfortunately it is next to impossible for him to keep abreast with the chemistry and pharmacologic properties of these preparations. Certainly the physician stands guilty if he does not know the dangers encountered in the thoughtless prescribing of these sedative agents, or if he permits his patients to continue their use unsupervised.

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DEFINITION

Sedative drugs may be defined as medicinal agents that tend to calm, to tranquillize or to allay irritability or pain. Most such agents, when employed in large amounts, have a hypnotic or soporific effect and produce sleep. Sedative drugs may be divided into two large groups, namely, (1) the sedative hypnotic group, and (2) the narcotic group (opium and its derivatives).

In this discussion I will not concern myself with the narcotic group as the use and abuse of narcotics is a problem quite apart from the use of other sedatives. All physicians realize the value of morphine and the dangers of its abuse, both with regard to the laity and their own occupational hazard. Marijuana (*Cannabis sativa*) in "reefers" constitutes a problem akin to that of morphine and is only mentioned to call attention to its gradual spread over the United States and Canada.

I will, however, consider the sedative hypnotic group of drugs in some detail. The number of sedative agents in use today is bewildering. Of special concern are the bromides and the barbiturates and I shall concern myself with these in the main but before closing shall mention chloral hydrate and paraldehyde briefly. Bromides have been employed in medical practice since soon after the discovery of bromine in 1826 by Balard. The barbiturates have been in use only since 1903 but today the array of derivatives of barbitol is so great that it is next to impossible to keep abreast with the new preparations that flood the market.

INCIDENCE OF USE

That sedative drugs are used extensively should need no special comment. Edie stated that of all drugs, sedatives are the most commonly used. This statement was written prior to the vitamin fad. Another common statement is that next to cathartics sedatives are the most commonly prescribed drugs. Edie went on to state that in 1936 about 1,250,000 doses of barbiturates went down American gullets. Hambourger's¹⁴ figures are similar. He found that more than 1,200,000,000 grains of barbituric acid derivatives were sold in the United States during 1936. According to one authority in England bromides rank fifth in the list of drugs most frequently prescribed. At this point it is fair to state that the use of sedative drugs has probably declined in recent years due to State and Federal drug regulations.

WHY THE ABUSE?

The extensive use of barbiturates and bromides just mentioned may rightly be assumed to indicate an abuse of these valuable

sedative drugs Just why is there such an abuse? The answer is not a simple one, as many factors play a role in the development of abuse. First of all, there is the factor of constitutional predisposition. Certain individuals seem to have an inherent tendency that renders them susceptible to habituation in one form or another As Ford has so well stated, "there are always those unfortunate individuals who need a crutch on which to limp through life" It is these persons who fall prey to sedative abuse as they do to excesses of any type At the moment the many psychologic adjustments precipitated by the war may well increase the demand for sedative medication on the part of "nervous" patients

Next there is the ease with which the patient can obtain a sedative drug In spite of legal restrictions patented nostrums containing bromides may be purchased "over the counter" or through mail order houses It is true that the number of such preparations on sale in drug stores has materially declined in recent years However bromide intoxication through self medication continues

At the time of introduction the barbiturates were generally supposed to be without toxic effects Certainly their beautiful array of colors might well allay any suspicion of possible harm. It was not long before it was recognized that the barbiturates might well become a two-edged sword Today about thirty states prohibit the sale of barbiturates without a physician's prescription, but barbitism continues

A point not to be overlooked is the advertising both for the bromides and for the barbiturates The pharmaceutical houses are not blameless in this matter Much of the advertising tends to confuse the physician and certainly lulls the layman into a feeling of security In fairness to most pharmaceutical houses it must be stated that detailed information concerning their sedative drugs is available Unfortunately, the busy physician only reads the head line on his new sedative sample which suggests a soothing sleep, but fails to recall that he is dealing with a powerful drug that may prove harmful to his patient.

Finally, the physician's responsibility must be stressed. The patient demands relief from real or imaginary discomfort and all too frequently it is easier for the doctor to prescribe rest and peace by the teaspoon, the pill or capsule than by hours of patient counsel

Sedative preparations, of course, are indicated and justifiably prescribed in many instances Regardless of the type of patient, the physician should supervise such sedative medication and not permit the patient to direct his own sedative treatment. Washburne emphasized the point that it is possible that many cases of bromism are the result of unsupervised medication following the prescribing

of bromides by the physician. The same situation may well apply in barbitalism.

INCIDENCE OF INTOXICATION

Figures relative to sedative abuse vary considerably. In a medical institution in which the staff is "drug conscious" the recognition and diagnosis of drug intoxication will be considerably higher than in a hospital in which the staff is less familiar with the problem. Such was the experience of Curran reporting from the Bellevue Psychiatric Hospital in 1939. In the ten year period from 1926 to 1936 the diagnosis of drug psychosis was made in 310 cases. In sixty-three it was due to bromides, in 114 to barbiturates, in twenty-one to both bromides and barbiturates and so forth. It is especially noteworthy that from September, 1936, to December, 1938, a little more than two years, the diagnosis of drug psychosis was made in 180 cases, as compared to the 310 in the preceding ten years. Levin, reporting from the Harrisburg State Hospital, found thirty-four cases of bromide delirium among 1,399 first admissions during a period of five years. According to Liebman and Richman the figures on bromide intoxication will vary from 1.5 to 4.7 per cent of hospital admissions. Blumer gave a much higher figure for psychopathic hospitals, namely, 5 to 10 per cent of admissions. In 1934, Scarlett and Macnab collected 408 deaths due to barbiturate intoxications. In 1939 and 1940 Hambourger^{14,15} in an extensive report of the promiscuous use of barbiturates stated that probably close to 300 suicidal deaths were caused by barbiturates in the United States in 1936 alone and that in 1937 the figure approached or even exceeded 400. Barbiturates, according to Hambourger, accounted for more than 10 per cent of all cases of addiction if alcohol were excluded. He went on to say, "The incidence clearly indicates that these drugs are responsible for many suicides, successful and attempted, as well as for many so-called accidental intoxications." Interestingly enough two-thirds of the addicts referred to by Hambourger claimed that they became familiar with the drugs through physicians.

Tod reporting from England noted that in 1,026 consecutive admissions, 38 per cent of the patients had received bromide medication. This figure closely approximates that noted in our local Rochester State Hospital.

The experience at the Mayo Clinic is rather unusual because of the relatively few cases of barbitalism as compared to the incidence of bromism. This disproportion is probably explained on the grounds that the majority of patients having barbitalism come from Rochester or the vicinity and that patients having severe barbitalism do not come from long distances seeking aid. Undoubtedly,

too many of the patients who had mild habituation did not reveal their addiction. The relatively large number of cases of bromide intoxication may be accounted for on the basis that in most instances the exact nature of the intoxication was not recognized prior to examination at the Clinic and in many instances the patients were transported from long distances in the belief that the patient suffered from some severe nervous disorder or from some intra cranial disease.

In the ten year period, 1934 to 1943 inclusive 158 cases of bromism and thirty eight cases of barbitalemia with findings referable to the central nervous system were encountered at the Clinic. Eleven per cent of these patients had used both bromides and barbiturates but the conditions were classed as bromide intoxication because of the known level of bromide in the blood. Patients who had only general physical manifestations as evidence of this intoxication are not included in these figures.

From this study it appears that females are more likely to have sedative habituation than males. Suicides did not occur among the group who had bromide poisoning but two deaths were attributed to bromide intoxication. It is rather interesting that in the majority of cases of bromism the use of the sedative resulted from the physician's unsupervised medication. In fourteen of the cases of bromism the source of intoxication was probably the well known "Blue" bottle. In spite of the small number of cases of barbitalemia three deaths were due to suicide, and in six additional cases suicide was attempted. There was one accidental intoxication in a child, aged two years. As far as could be determined a large percentage of the cases of barbitalemia resulted from self medication.

DANGERS OF SEDATIVE ABUSE

That serious dangers are associated with the abuse of sedative drugs is well recognized. In their proper place sedatives are, indeed, helpful and so used are not to be condemned. In certain instances small doses taken over extended periods of time would appear to be justified and seemingly have little, if any, harmful effects. I have reference especially to the use of phenobarbital or bromides in convulsive disorders. It should be remembered that nonanalgesic hypnotics given in the presence of pain may result in delirium.

The symptoms of abuse of sedatives may be divided into general symptoms and those affecting the central nervous system. In this discussion I shall only mention the more symptoms but shall stress symptoms referable to the central nervous system.

BROMIDE INTOXICATION

I shall consider the effects of bromide intoxication. Brown Sequard receives credit for advising the early intensive use of bromides. It is noteworthy that as early as 1877 Seguin wrote feelingly on the abuse and use of bromides.

Acute bromide poisoning is rare as the bromides are excreted rapidly at first and serious symptoms do not appear until the level of bromides in the blood becomes high. Chronic bromide poisoning is more common. A severe reaction may develop in the course of long-continued use of bromides and result in stupor, coma, respiratory impairment and cardiac collapse. Even death may eventuate.

In chronic bromide intoxication (bromism) the general physical symptoms may be outlined as follows: (1) those referable to the skin are acne, erythema, urticaria, pruritus, ulcers (bromoderma), (2) those from the gastro-intestinal tract are coated tongue, foul breath and anorexia, (3) those from the respiratory tract are coryza and pulmonary edema, (4) those referable to the heart are tachycardia and cardiac collapse and (5) those referable to the nervous system consist of neurologic and psychiatric manifestations.

As a rule, symptoms of bromide intoxication referable to the central nervous system develop insidiously and, as pointed out by Frugoni and Walsh, are often mistakenly attributed to exacerbations of the condition for which the medication was given. Increasing lassitude develops gradually with slowing of mental and physical faculties. These early symptoms may be readily mistaken for the onset of encephalitis, general paralysis of the insane or some other intracranial disturbance.

With continuation of medication the drowsiness may give way to irritability, increasing mental confusion, confabulation, disorientation, hallucinations and delusions. Curran considered delirium as the most common type of bromide psychosis. In this state the subject is usually disoriented for time and place. Hallucinations are of visual and auditory character and may be amusing or terrifying. Mention is repeatedly made in the literature regarding the visual hallucinations involving a brown or black color. This is not always the case, at least such information is not volunteered by the patient. Washburne and others called attention to the Lilliputian and Gargantuan hallucinations. The delusions also take on a terrifying character and may change from day to day. There may be fear of impending disaster or the patient may be convinced that some relative is being tortured in an adjoining room. The neurologic and the psychiatric symptoms may be listed as follows:

Neurologic Symptoms

Restlessness
Tremor
Muscle twitchings
Double vision
Dysphagia
Dysarthria
Ataxia
Diminished or abolished deep reflexes

Psychiatric Symptoms

Early symptoms
Irritability
Restlessness
Drowsiness
Late symptoms
Clouding of consciousness
Confabulation
Disorientation
Hallucinations
Delusions
Delirium (coma)

Diagnosis—The diagnosis of a bromide psychosis is usually relatively simply if the possibility of such a condition is kept in mind. All too frequently patients come to the physician or are brought to him because they *seem* to have some organic disease and the possibility of bromism has not been considered. It is not enough to inquire about the use of bromides as too frequently the patient's replies cannot be depended on and the relatives may not be aware that the patient has been taking bromides. On several occasions a negative reply was received in response to the question on medication but when the patient was asked about tonics he or his family readily admitted that he had used several bottles of a special salty nerve tonic that had been prescribed by the doctor.

The level of the bromides in the blood establishes the diagnosis. It is more or less accepted, as pointed out by Campbell, that a bromide level of 100 to 150 mg. per 100 c.c. of blood is sufficient to produce mild nervous manifestations of intoxication. When the content in the blood is from 150 to 250 mg per 100 c.c. weakness, restlessness, thick speech, irritability, hallucinations and ideas of reference may develop. When it is 250 mg or more per 100 c.c. of blood, symptoms of severe toxic psychosis will develop. These figures are not too constant as many individuals will tolerate a high concentration of bromides in the blood without evidence of intoxication. On the other hand, aged, arteriosclerotic individuals, patients suffering with disease of the kidney and patients after operations do not tolerate bromide medication well.

Differential Diagnosis.—In the differential diagnosis of bromism it must be remembered that bromide rash which is so helpful in making a diagnosis need not be present. Encephalitis paresis, affective psychosis, psychosis with organic disease, tumor of the brain and so forth are conditions which may be confused with bromism.

Treatment—The treatment of bromide intoxication consists of the elimination of bromides from the body as rapidly as it is possible. In the presence of mild intoxication it may suffice to discon-

tinue the bromide medication. In the more severe cases of intoxication elimination of the bromides is accomplished by frequent gastric lavage, the administration of sodium chloride and by supplying the body with adequate fluids. If the patient is co-operative, from 4 to 8 gm. of sodium chloride may be given by mouth in enteric coated tablets daily. In addition, Campbell advised the use of adrenal cortical hormone (eschatin) which, he considered, hastened recovery. Occasionally it will be necessary to give the saline solution intravenously. If fluids are given by nasal tube, care must be exercised because of the absence of the gag reflex. More than 4,000 c.c. of fluid should be given per day. A high caloric, high vitamin diet is important and may be administered by nasal tube. Sedatives should be avoided as much as possible. It is much better to resort to tepid baths, warm packs and ample nursing care. The duration of the psychosis varies and depends to some degree on the stability of the individual. The psychosis does not always bear a direct relationship to the bromide concentration in the blood. Thus, Claiborne noted as much as 350 mg. of bromide in the blood without mental symptoms. Occasionally the psychosis may clear up entirely in the course of one to two weeks, at other times the bromides appear to be excreted slowly and the mental symptoms may persist for six to eight weeks or even longer.

BARBITURATE INTOXICATION

The unique sedative qualities of the barbiturates have made them immediate and lasting favorites. Their apparent harmlessness and ease of administration were conducive at first to carelessness on the part of the physician in recommending their use and in their willing acceptance on the part of the laity. Not long after their introduction, however, it was recognized that the barbitol derivatives were not free of toxicologic dangers, which might range from a slight skin rash to a means of self-extinction.

Barbiturate intoxication differs from bromide intoxication in that the ill effects on the central nervous system usually far overshadow the general systemic manifestations. The symptoms of intoxication (barbitism) may be divided into three groups: those from (1) simple intoxication, (2) acute poisoning, and (3) chronic intoxication.

In simple barbiturate intoxication symptoms of poisoning are mild. Such symptoms may develop in individuals who are sensitive to the drug or who have taken an excessive amount within a short space of time. These symptoms are of a transitory nature and consist of drowsiness and at times of excitement with variable mild neurologic signs. As a rule, these effects are not serious and will

pass off in the course of six to twenty four hours and need cause no great concern. However, they serve as a warning to physician and patient that the use of barbiturates is not without danger.

Acute barbiturate poisoning follows the ingestion of large amounts of barbiturates either by accident or with suicidal intent. In such an event coma which may be preceded by a period of excitement develops rapidly. Depression of all bodily function accompanies the coma. The slow and shallow respiration indicates fairly well the degree of intoxication. The coma may persist for several days and end in recovery or death. During the stage of coma the body temperature falls, marked capillary dilatation occurs with drop in blood pressure and weak, rapid pulse. The deep reflexes may be entirely abolished and the Babinski sign may be positive.

If death occurs from one of the short acting drugs, it is usually due to respiratory failure. Death from the longer acting drugs such as phenobarbital is due to pulmonary edema, pneumonia and shock.

In the event of return of consciousness, neurologic signs become more manifest as nystagmus, slurred speech, tremor, ataxia and occasionally convulsions. Mentally the patient may remain dull and confused or be excited and euphoric. Occasionally a dreamlike state may persist for some hours or days.

Chronic Barbiturate Intoxication—The systemic manifestations in chronic barbiturate intoxication may include cutaneous disturbances some of which may be serious. Barefoot recently collected thirteen cases of exfoliative dermatitis with ten deaths and added a case of his own to the series. Gastro-intestinal, respiratory and cardiovascular disorders are encountered at times. The question of agranulocytic anemia resulting from barbiturate intoxication remains a moot question. Recently Hoagland called attention to the fact that in cases of acute porphyria the patients may give a history of having taken one of the aliphatic hypnotics. The general manifestations in chronic barbitarism may be listed as follows:

Skin

Rash (erythema)

Dermatitis

Angioneurotic edema

Gastro-Intestinal tract

Anorexia

Weight loss

Constipation

Respiratory tract

Asthma

Depression of respiration

Pneumonia

- Cardiovascular system
 - Fall in blood pressure
 - Dilatation of peripheral capillaries
 - Pulse weak and rapid
 - Shock
- Blood
 - Anemia (agranulocytic anemia)
- Miscellaneous manifestations
 - Acute porphyria
- Central nervous system
 - Neurologic manifestations
 - Mental manifestations

The neuropsychiatric manifestations in chronic barbitalsm will vary with the degree of intoxication and with the mental make-up of the patient. In severe intoxication the patient will exhibit increasing drowsiness and difficulty in concentration. An insidious change in the personality appears with carelessness and a wanton disregard for responsibility. Disorientation is commonly present. Cyanosis, nausea and vomiting may occur. The speech becomes thick, nystagmus is usually demonstrable and ataxia in some degree makes its appearance. These later symptoms are of cerebellar origin and are usually more profound than in cases of bromism. Occasionally convulsions occur though it is probably more common to have convulsions appear from two to six days following abrupt withdrawal of the barbiturate. Kalinowsky and Brownstein and Pacella have called attention to this fact even in nonepileptic patients. Hallucinations may develop especially if the patient has taken in addition to the barbiturate other sedative drugs as bromides or alcohol. The delirium so characteristic of bromism is not commonly encountered in barbitalsm. Manifestations referable to the central nervous system in chronic barbitalsm may be tabulated as follows:

Neurologic Manifestations

- Nystagmus
- Speech disturbance
- Tremors
- Ataxia
- Depressed reflexes
- Positive Babinski signs
- Convulsions

Mental Manifestations

- Drowsiness
- Lack of concentration
- Confusion
- Change in personality
 - Carelessness
 - Silly behavior
 - Irritability
- Disorientation
- Hallucinations
- Delusions
- Dream states
- Euphoria
- Excitement

Diagnosis—The diagnosis of chronic barbiturate intoxication should not be difficult if its presence is kept in mind. At times a person may be brought to the physician without any previous history of barbiturate use to guide him in the diagnosis. In such instances the diagnosis may be difficult if drug intoxication is not suspected. A positive diagnosis may be made by demonstrating the presence of barbiturates in the urine or in the gastric contents. The so-called Koppányi test while very accurate is complicated and time consuming as compared to the gold chloride test for bromides.

Differential Diagnosis.—Among the more common conditions to be considered under the heading of differential diagnosis are general paresis, encephalitis, multiple sclerosis, cerebral vascular lesion, tumor of the brain and finally acute psychosis, either of toxic or other origin.

Treatment.—In most instances withdrawal of the drug suffices in the treatment of barbiturate intoxication. If the drug has been taken over a long period the patient's general nutrition may need special attention. In severe cases of acute intoxication rather drastic measures of treatment may have to be instituted. All sedatives should be stopped at once and in their place hydrotherapy should be resorted to if there is excitement or an acute manic reaction. Fantus recommended gastric lavage with warm saline solution. He then inserted 30 to 60 gm. of magnesium sulfate by tube, taking special precautions to prevent aspiration pneumonia. Hot coffee enemas 5 per cent dextrose given intravenously, and 0.5 gm. of caffeine with sodium benzoate given intramuscularly every two hours alternating with injections of strychnine are among recommendations to be seriously considered in these cases. Reese advocated the intravenous administration of 5 to 11 c.c. of a 25 per cent aqueous solution of coramine to stimulate the respiratory centers if there is evidence of marked depression.

CHLORAL HYDRATE AND PARALDEHYDE

Of the other sedative drugs mention should be made especially of chloral hydrate and paraldehyde which have fallen into undeserved disuse.

Chloral Hydrate.—Chloral hydrate, like morphine, is one of the oldest hypnotic agents. It is a reliable sedative and is especially useful in the management of agitated states and convulsive seizures. It may be administered by mouth or by rectum in amounts up to 3 gm. (45 grains). Chloral hydrate has a disagreeable taste and it produces some gastric irritation. To overcome this it may be given as an elixir.

Addiction to chloral hydrate is not common, but when it does occur, the affected patient presents the symptoms of chronic alcoholism. Its use in "Mickey Finns" (knock-out drops) is probably more fictitious than real.

Acute poisoning from chloral hydrate is relatively rare. When it does occur, death may ensue within a few hours. In acute poisoning the pupils are contracted as with morphine. Cardiac collapse and death may ensue. Treatment of acute poisoning consists of lavage of the stomach, the intravenous use of glucose and the treatment of shock.

Paraldehyde—Paraldehyde is a safe and efficient hypnotic with low toxicity. In spite of its tendency to produce gastric irritation, it probably deserves a wider use than it enjoys at present. The fact that it has an offensive odor should be of distinct advantage and safeguard against its abuse. It may be administered by mouth or by rectum, it rarely should be used intravenously, except in skilled hands, as occasionally its use may be associated with acute circulatory collapse or pulmonary edema. In spite of its unpleasant and disagreeable odor, habit formation may occur. The symptoms of habituation are those of chronic alcoholism. Loss of appetite, anorexia, muscular weakness and a gradually developing delirium occur. The diagnosis of paraldehyde intoxication usually is made from the odor that is associated with it.

The treatment of acute paraldehyde poisoning consists in generously lavaging the stomach. The same measures should be used to support respiration and blood pressure as for barbitarism. Intravenous administration of glucose is of aid in assisting the circulation while supplying glycogen to protect the liver and to aid in diuresis.

PROPER USAGE OF SEDATIVE DRUGS

From this discussion it might be assumed that the use of sedative drugs is to be condemned. The presentation of such a view is not the intention of this review. It is, however, important to have a critical attitude concerning the use of sedatives and all must be willing to acknowledge that these drugs have a limited and special place in the practice of medicine. It has been implied that some of the sedative drugs, especially barbiturates, lack toxicity and may be prescribed without mental reservation on the part of the physician. This, of course, is not correct. Sedative drugs should be used primarily for symptomatic relief and as soon as possible their use should be discontinued and the patient should never be permitted to use them without supervision. If we physicians fully appreciate the dangers associated with sedative medication, few

of us would willingly discard them. In 1939, Karnosh did sound a word of optimism when he stated that the medical profession was exhibiting a distinct tendency to veer away from the abuse of sedatives. Unfortunately, the war with its psychologic upheavals may retard this favorable progress.

Some of the more common uses of sedative drugs that seem justifiable are as follows: in the treatment of convulsive disorders, as in epilepsy, convulsions owing to strychnine, tetanus and eclampsia, acute psychotic states associated with excitement and marked agitation, in cases of acute and transitory insomnia in tension states and in other nervous disorders directly under the supervision of a competent physician. In certain gastro intestinal disorders, such as spastic colitis, sedatives may have a place.

The moderate use of sedative drugs in hypertension is recommended by many physicians. Their use in preoperative care and postoperative care and in obstetrical practice seems definitely indicated. Occasionally in conjunction with analgesics they may be employed over brief periods of time, as the sedative may enhance the effect of the analgesia. Delayed sedative action by the use of the so-called "time bomb" introduced by Billings in which a sedative drug is given in an enteric coated pill or capsule may also be justified when carefully supervised.

The continued use of sedative drugs is usually contraindicated in prolonged psychic illnesses. Among patients who have unstable nervous systems their use should be avoided for fear of habituation. In renal disease and also in hepatic disease their use is contraindicated. This is especially true of the barbiturates which are detoxified in the liver. Other conditions in which the barbiturates should be used sparingly are hyperthyroidism, diabetes, severe anemias, cardiac failure and throughout pregnancy. The aged, senile and arteriosclerotic individuals do not tolerate sedative drugs well.

In conclusion I wish to emphasize that we physicians should bear in mind that sedative drugs serve a definite purpose and we should attempt to limit their use as much as is possible. Before prescribing them we should know the mental make-up of our patient as many individuals are so psychologically constituted that temporary relief from pain or worry may prove a stepping stone to habituation. While it is gratifying that there are laws concerning the dispensing of barbiturates and the labelling of other sedative drugs, more stringent regulations would seem to be necessary to curtail the use of some of the sedatives such as bromides which are still available on the open shelves in drug stores and through mail-order houses.

Finally, if we bear these warnings in mind we might paraphrase

about sedative drugs what Sydenham said so well about opium
Thanks to Almighty God for the remedies He has given us to quiet
the sufferings of man

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PENICILLIN IN THE TREATMENT OF SYPHILIS

PAUL A. O'LEARY

SINCE Mahoney, Arnold and Harris¹ demonstrated in June, 1943, that penicillin was of value in the treatment of syphilis, an intensive and extensive appraisal of the remedy has been undertaken under governmental supervision in a manner that is unique in the annals of medicine. Whether or not the plan of governmental control of such a study is looked upon with favor, it nonetheless must be admitted that it offered an exceptional opportunity to treat and observe many cases. Penicillin arrived in the field of syphilotherapy at a most propitious time, that is, when efforts were being directed toward the winning of the war and when governmental control and supervision of the study made possible in a remarkably short time the collection of a large number of case records and data on the results of treatment. Our present knowledge of the value of penicillin in the treatment of syphilis is still meager in spite of the collaborative studies, and the points I shall consider now are only preliminary impressions some of which undoubtedly will be changed in the near future.

As a wartime measure, the National Research Council revived a subcommittee on venereal diseases and assigned to it the task of determining the value of penicillin in the treatment of gonorrhea and syphilis. This subcommittee selected approximately twenty five clinics in this country to participate in the study, it furnished them penicillin and outlined the treatment program they were to employ in cases of acute syphilis. As the supply of penicillin was limited and since the medical departments of the Army and Navy demanded a rapid appraisal of its value and as acute syphilis was prevalent and on the increase all over the country, it was not long before many thousands of syphilitic patients had been treated and the "success" and "failure" records accumulated.

EARLY SYPHILIS

My early experience in the treatment of acute syphilis with penicillin was greatly influenced by the work of Herrell¹ and of Heilman who since 1941 have been studying the effect of penicillin in various infectious diseases. They have shown that when penicillin is administered intravenously, the required dose is only a third or a half of the dose required for intramuscular administration. They also had demonstrated that a concentration of 0.06 Oxford units of

penicillin per cubic centimeter of serum is most efficient for the treatment of certain infectious diseases. At the Clinic, we began the treatment of early syphilis by the continuous intravenous administration of penicillin by the drip method in December, 1943. We endeavored to maintain a concentration of penicillin in the serum of 0.06 units per cubic centimeter of serum. In spite of the technical difficulties, I agree with Sir Alexander Fleming that in cases of early syphilis the results of intravenous administration of penicillin are superior to those obtained by intramuscular injection.

It has been known for some time that, in cases in which syphilis is treated with arsphenamine, it is not the concentration of arsenic in the serum that determines the incidence of cure. In other words, arsphenamine is not exclusively spirocheticidal in its effects. The first impressions gained in regard to the mode of action of penicillin in cases of syphilis were that its effect would be spirocheticidal and its value would depend upon its ability to destroy readily all *Spirochaeta pallida* in the patient. Our early studies demonstrated the fallacy of this idea. In other words, it is apparent that a high percentage of patients who have early syphilis derive the maximal benefit when a total of 2,400,000 units of penicillin is administered intramuscularly in 75 days, at the rate of 40,000 units every three hours. If larger doses of penicillin are given, if the interval between injections is decreased, or even if a total dose as high as 15,000,000 units is administered, the incidence of successful results is not increased proportionately. Accordingly, we are now, after two and a half years' experience with penicillin, confronted with facts similar to those that took us twenty-five years to learn about arsphenamine, namely, that the factors which are of paramount importance in determining the results of treatment are not only the dose, the interval between injections, the manner of administration and the brand of the drug but the activity of the "defense mechanism" of each individual patient, and the rapidity with which the *Spirochaeta pallida* becomes resistant to the penicillin.

The period of observation after treatment of the patients who have been given penicillin is so short that it is impossible to speak in terms of cure. It is possible, however, to consider our early experiences and some of the failures.

After an injection of penicillin, the *Spirochaeta pallida* disappears rapidly from a chancre or moist papule. One type of failure that may be observed is the recurrence of moist papules which teem with spirochetes (clinical relapse). In cases in which the treatment is successful, the serologic tests become less positive and eventually become negative by approximately the ninth month after treatment is discontinued. Accompanying this decrease in the posi-

of the serologic tests, there is a corresponding decrease in the syphilitic amboceptor. In cases in which the treatment is successful, both the positiveness of serologic tests and the syphilitic amboceptor may decrease for a time relatively for a period and then begin to increase (serologic relapse). In such cases, reappearance of the infectious lesions (clinical relapse) may be anticipated. In 50 per cent of cases in which the total dose of penicillin was 600 000 units, and serologic relapse occurred within six months after treatment was discontinued.

During the dose so that a total of 2 400 000 units was administered over seven days produced a corresponding increase in the rate of cure. The minimal number of failures (25 to 35 per cent) occurred when this dose was employed. Since a relapse occurred in from 25 to 35 per cent of the cases in which a dose of 2 400 000 units was administered, it is evident that the use of penicillin alone does not comprise an adequate method of treating early syphilis.

In January, 1944 I started to employ a course of treatment in which penicillin, oxophenarsine hydrochloride (mapharsen) and bismuth was administered. More recently I have increased my enthusiasm for this type of treatment by employing two courses in certain cases of early syphilis.

At present, we are using the following plan of treatment in cases of early syphilis observed at the Clinic. A daily dose of 0.04 gm oxophenarsine hydrochloride is administered intravenously for 10 days. Starting on the fifth day, 40 000 units of penicillin is administered intramuscularly every three hours until a total dose of 2 000 000 units has been administered. Starting on the thirteenth day a dose of $1\frac{1}{2}$ grain (0.1 gm) of bismuth subsalicylate, suspended in 1 c.c. of a fixed oil, is injected intramuscularly every three days until twenty injections have been administered. The entire course will require about a hundred and thirteen days.

If a clinical relapse does not occur during the first three months after the completion of the course of treatment and if the reaction to serologic tests and the titer of the syphilitic amboceptor show evidence of reduction, the course of treatment is not repeated but the patient is kept under observation. If on the other hand, a clinical relapse occurs and if the reaction to serologic tests and the titer of the syphilitic amboceptor are first reduced but later increased, the course of treatment is repeated. Although we have not observed any failures it should be emphasized that the number of cases in which this type of treatment has been used is comparatively small and the average time that has elapsed since completion of the treatment is short.

The high incidence of reinfection in cases in which early syphilis has been treated with penicillin is evidence of the spirocheticidal effect of this agent. In fact, the terms "ping-pong syphilis" and "tennis syphilis" have been used to designate certain types of reinfection which are rather commonly observed in venereal disease clinics. In cases of ping-pong or tennis syphilis, the husband acquires the disease extramaritally and infects his wife before he knows that he has the disease. After administration of penicillin has produced a rapid involution of his lesions and has caused serologic tests for syphilis to become negative, the husband resumes his marital relations and is reinfected by his wife.

I am not in accord with syphilologists who believe that the treatment of early syphilis should be regimented or systematized. It seems to me that individualization of the treatment in cases of early syphilis is just as necessary as it is in cases of late syphilis. Experience has demonstrated that certain patients who have early syphilis can be cured by a few injections of arsphenamine while others fail to obtain a cure after hundreds of injections of preparations of arsenic and bismuth. I have observed a similar situation in cases in which penicillin has been used, that is, certain patients have been cured with 600,000 units of penicillin while in other cases the administration of 6,000,000 units has failed to cure the disease. I believe that it is necessary to treat each patient according to his needs, if one course produces satisfactory results, there is no need to continue the treatment indefinitely.

Penicillin produces few complications. Urticaria which lasts from seven to ten days, may be troublesome. A few persons who have worked with penicillin have become sensitized to it and a vesicular eruption of the hands, similar to the "id" reactions of trichophytosis, has developed in a few cases in which penicillin has been administered. Febrile reactions that develop during treatment are usually due to an impurity in the drug, to improper sterilization of the water or to faulty preparation of the physiologic salt solution. In cases in which administration of arsphenamine has caused an exfoliative reaction, penicillin must be administered with great caution because it may cause a recurrence of the dermatitis. Likewise, local applications of penicillin ointment may produce a dermatitis which will recur in a more severe form if penicillin is administered by intramuscular injection several months later. Hemorrhagic encephalitis has been reported to have occurred in some cases in which penicillin has been administered concurrently with the daily injection of large doses of oxophenarsine hydrochloride (mapharsen) for a long time. In some cases, the hemorrhagic encephalitis has been fatal. In such cases, the hemorrhagic encephalitis is the

result of the oxophenarsine hydrochloride and is not attributable to the penicillin. One of the reasons for the increasing use of penicillin in cases of syphilis is the comparative absence of serious complications following its administration.

LATE SYPHILIS

In the treatment of *late cutaneous syphilis*, the effects of the administration of penicillin are dramatic. After the intramuscular administration of 1,500,000 units in seven days, the ulcerative and nodular lesions heal rapidly and the serologic response tends to become negative in from twelve to fifteen months after treatment has been discontinued. If no other manifestations of syphilis are present, I have found one such course of penicillin given alone to be sufficient.

Even more dramatic are the results noted in cases of *osseous syphilis*. I refer especially to cases of gumma of the nasal septum and roof of the mouth, in which the effect of penicillin is twofold: that is, it not only controls the syphilitic process but also overwhelms the anaerobic secondary invaders present in such lesions. Physicians who have experienced the therapeutic resistance or so-called arsphenamine fastness of lesions of this type under the old arsphenamine-bismuth regime will be struck by the dual effect of penicillin in such cases. The same is true of periostitis and osteitis of the tibia.

A similar degree of enthusiasm is warranted in cases in which *visceral syphilis* involves the liver and stomach. The effects of penicillin are more rapid and thus far appear to be associated with fewer complications than the results obtained with the methods of treatment formerly used in such cases. The decrease in time required for treatment also is significant. It is my practice to administer 10,000 units of penicillin every three hours for ten days. If advisable, a second course may be given after an interval of six to eight weeks has been permitted to elapse. Longer observation of the patients is necessary before final conclusions are permissible as to the superiority of penicillin in the treatment of syphilis of the stomach or liver, but my experience with it thus far is most encouraging.

Unfortunately at this time, the same thing cannot be said for the value of penicillin in the treatment of *cardiovascular syphilis*. I have heard of several cases of syphilitic aortitis and aortic regurgitation in which the patients died immediately after the intramuscular injection of penicillin. At least five years of treatment and observation of patients with cardiovascular syphilis will be necessary before deductions as to the value of this drug will be justified.

If penicillin is to be administered in cases of syphilitic disease of the aorta, the patients should be kept in bed, and small doses, not more than 5,000 units, of penicillin should be administered intramuscularly for a long time. My experience at this time is entirely inadequate to permit of any predictions as to the value of penicillin in the treatment of cardiovascular syphilis.

NEUROSYPHILIS

In the investigation of penicillin, I was requested to study its value in the treatment of neurosyphilis, therefore, I have been particularly interested in this phase of the subject. I am sorry to report that my experience with the use of penicillin in the treatment of this type of syphilis has been disappointing in many respects. One favorable effect has been noted, that is, when penicillin is administered in the early stage of syphilis it appears to decrease the incidence of *asymptomatic neurosyphilis*. In from 15 to 25 per cent of the cases of early syphilis in which the patients have been treated with arsphenamine and bismuth at the Clinic, examination of the cerebrospinal fluid has disclosed an increase in the cell count, an increase in the concentration of protein and a positive complement fixation reaction for syphilis. In the absence of clinical evidence of neurologic involvement, these findings are considered indicative of asymptomatic neurosyphilis. Thus far, such evidence of asymptomatic neurosyphilis has been obtained in only about 4 per cent of cases of early syphilis in which the patients have been treated with penicillin at the Clinic.

In about 20 per cent of the cases of early and late asymptomatic neurosyphilis in which penicillin has been administered, the drug caused the spinal fluid to return to normal. In about two thirds of the remaining cases, the administration of penicillin produced a reduction in the cell count, in the concentration of protein and in the reaction to Lange's colloidal gold test although the reaction of the cerebrospinal fluid to complement fixation tests for syphilis remained strongly positive. Further observation is necessary before definite statements can be made regarding the value of penicillin in the treatment of asymptomatic neurosyphilis.

Penicillin produces two outstanding effects in cases of *tapes dorsalis*: (1) the patients gain approximately 15 pounds (6.8 kg), and (2) about 25 per cent of the patients notice a temporary decrease in the lightning pains. The changes that have been observed in the spinal fluid after the administration of penicillin in cases of locomotor ataxia have consisted mainly of a reduction of the cell count and a decrease in the concentration of protein. I have not

observed any improvement in such clinical symptoms as gastric crisis, vesical and rectal incontinence, Charcot's joints and ataxia

In cases of *general paresis*, the only benefit that can be attributed to the use of penicillin is a slight gain in weight. The same thing can be said of the use of penicillin in the meningovascular and vascular types of neurosyphilis. In cases of early paresis in which changes in personality irritability nervousness, forgetfulness and tremor of the lips have been present, I have not observed any improvement in the psychic reactions of the patients after the administration of penicillin.

The administration of penicillin has proved more satisfactory in *meningeal syphilis* than it has in other types of neurosyphilis. In cases of meningeal syphilis, penicillin produces an improvement in such symptoms as headache, nausea, convulsions and coma, and it also causes an improvement in the changes in the cerebrospinal fluid. In this connection it should be mentioned that this type of neurosyphilis has been highly responsive to the older methods of treatment.

Penicillin does have a favorable "tonic" effect in some of the parenchymatous types of neurosyphilis, however this effect is not as noticeable as it is after fever therapy has been used.

Although it is too early to compare the value of penicillin with that of other methods used in the treatment of neurosyphilis, my experience indicates that penicillin produces clinical improvement in from 15 to 20 per cent of cases while fever therapy produces improvement in from 60 to 80 per cent of cases.

In cases of neurosyphilis I have administered penicillin in different ways and by a combination of methods. I have administered as much as 6 000 000 units per week in some cases. The intravenous method of administration has produced the best results. Intraspinal administration of penicillin in combination with the intravenous or intramuscular injection of this agent has also been successful. When penicillin is combined with malarial therapy or fever therapy the results are the same as those obtained with malarial therapy or fever therapy alone.

CONGENITAL SYPHILIS

Thus far, penicillin has appeared to be of value in the prevention of *congenital syphilis*; likewise, it has been successful in the treatment of a high percentage of infants who have had congenital syphilis. However as the affected children become older the results are less encouraging. In the treatment of interstitial keratitis in which the results of other investigators have at best been variable, my experience with penicillin has been most unsuccessful. Neuro-

syphilis of the congenital type also has been unresponsive to penicillin therapy

COMMENT

Penicillin is now being administered in a variety of ways, such as by injection in oil, by mouth and by inhalation. None of these methods has as yet had sufficient trial in cases of syphilis to warrant any conclusion regarding the best method of administration. The evaluation of penicillin in the treatment of syphilis is still in a fluid state. The fact that it is possible to produce a satisfactory concentration of penicillin in the blood serum by administering four or five times as much by mouth as is administered parenterally is highly significant. A study of the treatment of syphilis by the oral administration of penicillin was started several months ago.

The information gained during the past two and a half years is only the groundwork for the future use of penicillin in syphilotherapy. It appears that the advances to come will be based on the experience which shows that penicillin is nontoxic, that it produces satisfactory clinical results quickly and that the successful treatment of early syphilis will be materially shortened. At this time information is accumulating which indicates that there are several different types of penicillin and several factors in it that exert different effects on the *Spirochaeta pallida*. One of these factors has been found to have only a slight spirocheticidal effect and its presence in penicillin may account for some of the variations in the therapeutic results. Thus far the drawbacks have been that hospitalization is necessary in cases in which penicillin is administered every three hours and it is not a panacea for all types of syphilis or for all persons who have syphilis. More than ever it seems that individualization of the treatment of syphilis is necessary and that syphilotherapy systematization and regimentation are no longer advisable.

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THE VALUE OF GASTROSCOPY IN THE DIAGNOSIS OF GASTRIC DISEASE

HERMAN J MOERSCH

GASTROSCOPY, although one of the oldest of the endoscopic procedures was one of the last to establish itself as an important diagnostic entity. It was only after the development of the flexible gastroscope by Wolf and Schindler in 1932 that gastroscopy received serious consideration as an adjunct to the methods available in the diagnosis of gastric disease. As frequently happens with the introduction of a new diagnostic procedure, many extravagant claims were advanced for the superiority of gastroscopy over other diagnostic aids. Unfortunately, it was not able to live up to such unwarranted claims and unjust criticisms were soon cast on the procedure. Time and experience, however, have demonstrated that gastroscopy, within its limitations has a useful and valuable place in the study of gastric disease.

Gastroscopy is not a procedure that should be employed in a haphazard manner as a possible short cut in diagnosis. Rather it should be used as an adjunct to other diagnostic measures. It should not, in my estimation, be employed routinely or in an indiscriminate manner, for even in the hands of the most skilled gastroscopist some slight risk is entailed in its use. There are certain contraindications to gastroscopy that must be constantly kept in mind. It should not be employed in the presence of severe cardiac or respiratory disease. Esophageal disease, deformities of the vertebral column, convulsive disorders and active gastric bleeding also contraindicate gastroscopic examination. Considerable discretion should be used in advising the procedure when patients are of advanced age, are greatly debilitated or are unstable from a nervous or emotional standpoint. It is especially advisable to postpone gastroscopy in the presence of an acute infection of the upper part of the respiratory tract.

There are many indications for gastroscopy. It should be considered in the case of any patient who complains of gastric distress when an adequate explanation of symptoms cannot be arrived at by other diagnostic means. It is of value when the diagnostic findings do not seem compatible with the clinical history or when the findings are not clear cut or definite. A field in which gastroscopy can be of considerable value is its use in collaboration with roentgenologic examination in the study of questionable gastric lesions. When it is used in such a manner it may lead to a correct diagnosis.

which otherwise might not be possible. Again gastroscopy may be of value in following the course of gastric disease both during its development and while the patient is under treatment.

It should be pointed out that, in the evaluation of gastroscopic findings, it is not usually possible to examine the interior of the stomach in its entirety. For mechanical reasons adequate visualization of certain regions of the stomach, especially the posterior wall and the lesser curvature beyond the angle, may be difficult or impossible. Excessive gastric secretion and gastric spasm may at times increase the difficulty of visualization. In the great majority of cases it is possible, however, to obtain a view of the interior of the stomach sufficiently adequate to enable one to reach a satisfactory diagnosis.

CARCINOMA OF THE STOMACH

Gastroscopy can be of definite value in the diagnosis of carcinoma of the stomach. It is at times possible to recognize a carcinoma of the stomach by gastroscopy when it has escaped detection by other diagnostic methods. While the experienced roentgenologist is able to recognize the majority of cases of carcinoma of the stomach on roentgenologic examination, a certain number will escape visualization. Whenever there is any question as to the diagnosis of carcinoma of the stomach gastroscopy should be employed, for not infrequently a carcinoma may be discovered which otherwise might go unrecognized. In order that gastroscopy may be of its greatest value in the study of carcinoma of the stomach, it is important that it be employed in close collaboration with roentgenologic examination. This is due to the fact that the roentgenologist may detect some slight alteration of the gastric pattern that is suggestive of the possibility of a gastric lesion but insufficient to enable him to establish a positive diagnosis even on repeated examinations. Often, by employing gastroscopy as an adjunct in cases of this type, a correct diagnosis may be established which otherwise might be impossible by either method alone. By combining gastroscopy with roentgenologic examination, earlier diagnosis of carcinoma of the stomach becomes a possibility.

Carcinoma of the stomach, as visualized through the gastroscope, presents all the variations seen in cases of carcinoma elsewhere in the body. Diffuse, infiltrating carcinoma of the stomach, such as is seen in *linitis plastica*, presents the greatest difficulty in differential diagnosis, because of the fact that there may be no normal gastric mucosa present for purposes of comparison. Palpation of the abdominal wall during gastroscopy is often of value in bringing a gastric lesion into view and aids in inspection of the lesion. It may also be of value in distinguishing between a benign and a malignant

lesion because carcinoma, as a rule, renders the gastric mucosa much less pliable than the normal mucosa

Schindler expressed the opinion that Borrmann's classification of carcinoma of the stomach is of value from the gastroscopic standpoint in determining the operability of gastric carcinoma. Although distant submucosal metastatic implants may be found on gastroscopy which otherwise might be overlooked and which might influence the prognosis, I am inclined to agree with Rodgers that gastroscopy is of but minor importance in determining the operability of carcinoma of the stomach. It is impossible to determine gastroscopically whether or not the carcinoma has extended through the serosa and involvement of glands or adjacent organs has taken place.

Although the diagnosis of carcinoma of the stomach can be made readily in most cases from the gastroscopic appearance of the lesion at times great difficulty may be experienced in determining the exact character of the lesion. Severe gastritis is the condition most likely to be confused with gastric carcinoma, especially gastritis of the *limitis plastica* type. Less frequently, difficulty may be experienced in distinguishing between a benign and a malignant ulcer. Lymphoblastomatous infiltration of the gastric mucosa as a rule closely simulates the infiltration seen in cases of carcinoma. Occasionally it is possible to distinguish between the two gastroscopically. This is especially true if there is other clinical evidence, such as glandular adenopathy or mediastinal widening, to suggest the possibility of lymphoblastoma. In lymphoblastomatous infiltration, the stomach is usually found much more pliable than in carcinoma and the infiltration is generally more diffuse with multiple small nodular regions of elevation scattered over the mucosal surface. If it is possible to distinguish between carcinoma and lymphoblastoma of the stomach, it may markedly influence the problem of treatment. Should the condition be lymphoblastoma roentgen therapy is the treatment of choice and generally brings about a prompt retrogression of the lesion. If the lesion is due to carcinoma surgical treatment is preferable. Gastroscopy is also of value in following the progress of a patient who has lymphoblastoma of the stomach and is under treatment, as it may give the first inkling of recurrence or reactivation of the lesion and thus bring about more prompt institution of therapeutic measures.

GASTRIC ULCER

Although the experienced roentgenologist has become very proficient in the diagnosis of gastric ulcer, there still remains a small percentage of cases in which the ulcer cannot be demonstrated by

this means. If the patient's symptoms are suggestive of gastric ulcer, even though the roentgenologic examination gives negative results, gastroscopy is indicated and not infrequently will uncover an unrecognized gastric ulcer.

Gastric ulcer as seen through the gastroscope presents a striking and characteristic picture. The ulcer usually has a well-defined border, which sharply demarcates it from the surrounding tissue. The base of the ulcer is covered with whitish gray debris and occasionally blood will be found oozing from the base. During the acute phase of the ulcer, the gastric mucosa about it becomes edematous, increasing the depth of the crater of the ulcer. With healing of the ulcer the surrounding edema subsides, with diminution of the depth of the crater and a decrease of the size of the ulcer. As healing progresses, the edges of the ulcer tend to advance toward the center of the crater. This process tends to throw the gastric mucosa into folds that resemble the spokes of a wheel. Care must be exercised to distinguish between true gastric ulcer and regions of superficial ulceration or erosion which frequently appear on the gastric mucosa. These latter regions of ulceration do not represent true gastric ulcers but a type of gastritis which pursues an entirely different course and has a different prognosis. It will be discussed further along with the various other forms of gastritis.

At times considerable difficulty may be experienced in distinguishing between benign and malignant ulcer. Gastroscopy may often be of considerable assistance in distinguishing between the two and thereby may influence the course of treatment. In contrast to benign gastric ulcer, a carcinomatous ulcer is generally characterized by a nodular infiltration of the gastric wall about the ulcer. The edges of the ulcer are ragged and not sharply demarcated from the surrounding tissue. The base of the ulcer is covered by dirty, necrotic debris, which may be bloodstained. As a rule, the two lesions can be readily distinguished from each other gastroscopically. At times, the correct differentiation must rest on microscopic examination.

If a patient is undergoing medical management for gastric ulcer, gastroscopy is of value in determining the response to treatment. The roentgenographic evidences of gastric ulcer will be found to disappear more rapidly than the gastroscopic evidences. This knowledge is of value in the better management of patients who are being treated medically and may lead to closer and longer observation with less likelihood of recurrence. It is also possible by this means to keep the ulcer under closer surveillance and thus detect any change that might be indicative of malignancy. Although a carcinomatous ulcer does not usually decrease in size roentgeno-

graphically on medical management, it may occasionally decrease and this fact constitutes another indication for gastroscopic follow up on gastric ulcers under medical treatment.

Gastroscopy is of no value in the diagnosis of duodenal ulcer

GASTRITIS

The exact role and significance of gastritis in the field of gastric disease have not been exactly defined. That gastritis should always be seriously considered in the case of any patient who has unexplained gastric distress is unquestioned. It is not within the province of this presentation to attempt to evaluate the clinical importance of gastritis but rather to point out the value of gastroscopy in its diagnosis. Gastroscopy is by far the most valuable and accurate method available at the present time in the diagnosis of gastritis. It enables the examiner to study the development, course and possible relationship of gastritis to other types of gastric disease.

From a gastroscopic standpoint, the changes that may occur in the gastric mucosa and be classified as gastritis are very numerous indeed. One of the most difficult problems at times is to determine where normal physiologic changes stop and gastritis begins. For purposes of classification gastritis is most conveniently divided into three main groups according to the classification devised by Schindler. These consist of superficial gastritis, hypertrophic gastritis and atrophic gastritis. Superficial gastritis is usually transitory, may disappear as rapidly as it appeared and may pass over into hypertrophic or atrophic forms. Transition from the hypertrophic to the atrophic type of gastritis is less common but may occur. At times all three types of gastritis may exist in the same person. One of the most interesting types of gastritis from the gastroscopic standpoint is erosive gastritis. Here one finds multiple small superficial erosions scattered over the stomach. These are sometimes mistaken for small gastric ulcers. Erosive gastritis may come and disappear very rapidly or may remain over long periods. It is regarded by some observers as a possible forerunner of true gastric ulcer and is frequently associated with gastric bleeding. Gastroscopy also allows the visual check of the response of gastritis to various types of treatment.

POSTOPERATIVE CONDITIONS OF THE STOMACH

The patient who has undergone an operation on the stomach and subsequently has gastric distress offers an extremely difficult diagnostic problem from both the clinical and the roentgenologic standpoints. Gastroscopy can be of considerable value in the study of these cases and can often offer the correct solution to the patient's

difficulty In most instances one can obtain a satisfactory view of the new stoma and often it is possible to secure an adequate view of the adjacent jejunum The stoma in a partial gastrectomy is generally more readily visualized than is that of a gastro-enterostomy A satisfactory view of the interior of the stomach and the stoma can be obtained on gastroscopic examination in more than 85 per cent of cases in which operation has been performed

In approximately 30 per cent of cases in which gastric distress develops following a gastric operation, the result of gastroscopic examination will be found entirely negative This is contrary to the usual teaching that all stomachs on which operation has been performed show evidence of gastritis In cases in which the result of gastroscopic examination has been found entirely negative, if measures directed toward neurogenic factors are instituted, frequently the patient's symptoms will promptly disappear In many cases of postoperative gastric distress gastroscopy will reveal severe gastritis, which often accounts for the patient's difficulty While the problem of treatment in this type of case is extremely difficult, often the reassurance given may be of some comfort to the patient and the physician The knowledge that gastritis may account for the symptoms may act as a deterrent to further gastric surgical treatment, which so frequently results in failure in this type of case Patients who have postoperative gastritis as a rule do not react as favorably to psychotherapy as those patients who have a normal gastric mucosa

Gastroscopy may be of value in detecting recurring gastric ulcer or carcinoma or give the first inkling of the development of new lesions of this type, which otherwise might be overlooked Gastrojejunal ulcer and jejunitis, which often are hard to detect on roentgenologic examination, may at times be found on gastroscopic examination Such lesions as benign tumors and foreign bodies may also be detected by this means A study of the function of the new stoma, so readily seen on gastroscopy, offers an interesting possibility as to the relationship of an adequately functioning stoma as a cause of gastric distress after operations on the stomach

UNEXPLAINED GASTRIC BLEEDING

The patient who has active bleeding from the stomach, or presents a history of such bleeding with no adequate explanation apparent from the clinical history or the usual routine diagnostic procedures, is an excellent candidate for gastroscopic study Gastroscopy may at times offer the correct explanation for such bleeding when all other diagnostic procedures have failed As a rule, gastroscopy should be postponed until active gastric bleeding has subsided

Among the lesions that may be found to account for gastric bleeding is an unidentified small gastric ulcer or carcinoma. Gastritis, especially of the erosive type, is often found to be the cause of unexplained bleeding. Less frequently, large veins may be noted in the cardiac end of the stomach and lead to the identification of esophageal varices and the establishment of the diagnosis of Banti's disease or hepatic cirrhosis. Bleeding may occur from gastric varices as well as from esophageal varices, although bleeding from the latter is much more common than from gastric varices. Benign tumor may occasionally be found as the underlying cause of gastric bleeding, with gastric syphilis or lymphoblastoma as less likely offenders. Foreign bodies such as phytobezoars, pieces of tubing, capsules and pills may be identified in the stomach and produce ulceration with bleeding. After operations on the stomach, in addition to the lesions just described, gastroduodenal ulcer and jejunitis may be found to account for gastric bleeding.

GASTRIC POLYPI AND BENIGN TUMORS

Gastric polypi and benign tumors, as a rule, are readily recognized on roentgenologic examination. Occasionally, however, such lesions, especially small polypi, may go unrecognized until discovered on gastroscopic examination. Gastroscopy may be of value in differential diagnosis between gastric polypi, benign tumors and malignant lesions. It may also be of value in following the course and progress of the lesions as they may undergo malignant change which may be detected at an early stage by direct visual inspection. It is not uncommon to find on gastroscopic examination that more gastric polypi are present than appear on roentgenologic examination alone. It is not possible, as a rule, to distinguish gastroscopically with exactness as to the exact microscopic character of benign gastric tumors.

GASTRIC SYPHILIS

This comparatively rare condition may tax the diagnostic acumen of the most careful clinician to the utmost. Gastroscopy, in conjunction with other diagnostic procedures, may be of value in establishing a correct diagnosis and even alone may give the first indication of the true underlying pathologic condition. From a gastroscopic standpoint, gastric syphilis may manifest itself in a variety of ways, dependent on the stage of the syphilitic process. The gastric mucosa in cases of syphilis generally presents a beefy red appearance. There may be infiltration of the gastric mucosa, which may be localized or diffuse and at times may be very extensive. The surface of the gastric mucosa may be studded with

multiple small papillary elevations producing a warty appearance. The regions of infiltration may break down and give rise to regions of ulceration, which are usually irregular in contour, vary in size and are usually associated with tumefaction. Again, gastric syphilis may produce considerable scarring in the wall of the stomach, causing contractures, and give rise to an hourglass deformity. In cases in which the diagnosis of syphilis can be confirmed, the appearance of the gastric mucosa undergoes rapid alteration under antisiphilitic therapy and may rapidly return to normal.

REDUNDANT GASTRIC MUCOSA

Redundant gastric mucosa may occasionally give rise to a picture that closely simulates that seen in cases of gastric carcinoma. If the redundant gastric mucosa is situated in the antral portion of the stomach and is of such proportion and attachment that it might prolapse into the pylorus, it could conceivably give rise to obstructive symptoms. Should the redundant mucosa, furthermore, be involved by gastritis, ulceration and bleeding with associated anemia might occur to complicate the picture further and add to the difficulty of differential diagnosis. If the redundant mucosa is confined to the body or cardiac end of the stomach, the condition is more likely to be asymptomatic than if it is located in the antral portion.

Gastroscopy may be of aid in the differential diagnosis should such a problem arise. The importance of such differentiation is self-evident, as redundant gastric mucosa seldom requires surgical intervention, whereas, if the condition is due to carcinoma, prompt surgical treatment is in order. A benign tumor attached to the gastric wall by a long pedicle might rarely be confused with prolapsed gastric mucosa.

CARCINOMA OF THE PANCREAS

Carcinoma of the pancreas, especially when it involves the body of the organ, offers one of the most difficult of diagnostic problems. From an anatomic standpoint, as Comfort and I have pointed out, gastroscopy should be of value in the recognition of such lesions. Since the stomach lies in intimate contact with the pancreas, a lesion arising in the pancreas and attaining size should cause an alteration of the contour of the adjacent gastric wall which it might be possible to recognize on gastroscopic examination. If a lesion arising in the pancreas infiltrates into and through the gastric wall with associated ulceration, it would be impossible to distinguish such a lesion from a primary gastric carcinoma from the gastroscopic standpoint alone. Clinical experience has demonstrated that in cer

tain cases the diagnosis of tumor of the body of the pancreas can be made on the basis of gastroscopic findings

GASTRIC VARICES

Under contraindications to gastroscopy it was stated that the procedure should not be employed in the presence of esophageal disease. This rule holds true in most instances. Recently, however, I have found that gastroscopy should be considered in cases of esophageal varices in which injection of the esophageal varices with a sclerosing solution is considered, in order to determine whether or not varices are present in the stomach. It has been my experience, in treating patients who have esophageal varices, that if varices are present also in the stomach, injection of the esophageal varices will very likely be followed by disappointing results. This is due to the fact that bleeding will continue from the gastric varices even though the esophageal varices have been eradicated. Although gastric varices can be identified in a high percentage of cases on roentgenologic examination, gastroscopy has been found more accurate in this respect than roentgenologic methods. So far I have not encountered any difficulty as a result of the examination, although it is not advisable to carry it out during an active phase of bleeding.

OTHER CONDITIONS

There are many other conditions involving the stomach in which gastroscopy may be of value in arriving at a diagnosis or a better understanding of the patient's symptoms. It may be of value in the identification and inspection of gastric diverticulum, tuberculosis, pernicious anemia and foreign bodies in the stomach. In my opinion it has only touched on a most useful field, namely the better understanding of gastric function. While much has been accomplished in the past, gastroscopy still has many fertile fields to explore.

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MEDICAL PROBLEMS IN CASES OF ACUTE ABDOMINAL PAIN

J M STICKNEY

THE problem of acute abdominal pain usually has been approached by attempting to make a positive diagnosis of a condition the treatment of which is known to be surgical and, failing in this to allow time and developments to establish the diagnosis. It is equally important to make a positive diagnosis of a disease the treatment of which is nonsurgical or medical.

A great number of diseases at some time in their course may produce severe and acute abdominal pain, the relief of which is not immediately surgical. Only those conditions which have been encountered recently on a general diagnostic hospital service at the Mayo Clinic will be discussed, which means that the problems raised are of practical importance.

It is essential that an adequate history be taken. The story of the onset, severity and progression of pain and associated vomiting and intestinal action is important but some knowledge of the patient's past illnesses and emotional problems together with an adequate inquiry into significant symptoms involving all the systems may bring out definite diagnostic data. Some estimate of the patient's threshold for pain may be made in the process of obtaining such a history.

In attempting to locate the origin of any abdominal pain a knowledge of anatomy and of the hypotheses about pain is of great aid. The abdominal wall is supplied by motor and sensory nerves originating in the sixth to the twelfth thoracic segments and the first lumbar segment of the spinal cord. The sixth to the ninth intercostal nerves supply the upper half of the rectus abdominis muscle and the tenth to the twelfth intercostal nerves and the ileohypogastric branch of the first lumbar nerve supply the lower half. The anterior portion of the parietal peritoneum is supplied by sensory branches of these same nerves. The lateral portions of the diaphragm are supplied by sensory branches of the thoracic nerves while the central portions are supplied by the phrenic nerves. The visceral peritoneum and the abdominal organs are supplied by the ramifications of the sympathetic nervous system and the nerves accompanying the vascular tree extending into the mesenteries.

Any serosal surfaces involved by an infectious process or any somatic structures previously damaged by trauma or infection are

likely to have a lowered threshold for pain. The threshold of older patients for pain is often higher than normal.

The problem of referred pain or the visceroparietal reflex has received much attention for many years. If the hypotheses of Lewis are accepted, the problem is fairly well defined since only one pathway from viscera to the spinal cord and reflexly to the parietal region supplied by the same segment is postulated. It becomes evident, then, that a similar type of pain may be produced no matter where in this reflex arc the disease is located. A disease affecting the nerve root at the twelfth thoracic level may produce pain similar to that produced by disease of the appendix. It is for this reason that other manifestations of disturbed visceral function, such as vomiting or abnormal intestinal action, are important in any analysis of pain.

The reviews by Jones have summarized clinical and experimental knowledge of the level at which distention or spasm of the abdominal viscera produces a sensation of pain. Beginning with pain produced substernally or in the shoulder and arm by lesions of the lower part of the esophagus, the site of pain becomes progressively lower in the abdomen as the site of origin descends in the gastrointestinal tract. In cases of renal and ureteral colic the perception of pain in the lumbar region and over the anterior abdominal wall to the testes is well known. It is possible to follow the course of a stone passing down the ureter by the location of the abdominal pain.

The differentiation of pain originating in the viscera from that caused by a lesion in the spinal cord or column is important. Eaton has discussed the diagnostic characteristics of root pain produced by tumors of the spinal cord or protruded intervertebral disks. Root pain is intensified by anything which increases intra-abdominal pressure such as coughing, sneezing or straining at stool. When the nerve roots are stretched, as in bending the head forward on the thorax or in straight leg raising, such pain is made worse. It is also likely to occur or be intensified during sleep. Arthritic changes in the spinal column, such as spondylitis and possibly osteo-arthritis and postural changes, such as scoliosis, may also account for a root type of pain. Vigorous pressure over the segment involved or a change of position may increase or may relieve it. In roentgenograms made at the proper level, changes in the spinal column may be demonstrated. A spinogram made with air or opaque material may be necessary to show tumors of the spinal cord. The presence of hyperesthesia and paresthesia in the region of the nerve distribution is deserving of study. It may last longer than pain, is variable and is not well understood in cases of referred pain.

Abdominal rigidity may occur just as readily with root pain affecting the abdomen as it may with referred visceral pain or direct irritation of the parietal peritoneum

Paravertebral block or local infiltration with anesthetic agents such as procaine hydrochloride or metycaine has been advocated recently for its aid in the diagnosis of the origin of pain. It should not be forgotten that such procedures will interrupt the visceroparietal reflex and therefore may abolish the pain of visceral disease as well as that of disease of the nerve roots

In addition to diseases localized in the viscera or about the exit of the nerve roots from the spinal column, those which primarily involve the nervous system itself, such as herpes zoster neuritis, pernicious anemia, infectious diseases and intoxications such as lead poisoning, will produce pain in the regions supplied by one or several peripheral nerves. With the exception of herpes zoster however there will always be other nervous and systemic manifestations of the disease

Severe abdominal pain may be associated with many vascular disorders. The extension of the pain associated with coronary insufficiency to the upper part of the abdomen is occasionally noted. The relationship to exertion in this type of pain is important. When occlusion occurs, the other signs of the condition and the electrocardiographic changes will be important, although the latter may not occur for many hours. An aneurysm of the aorta may dissect rapidly or slowly. If the dissection is rapid, the pain will shift. In a slower process evidence of deposits of calcium in the wall of the aneurysm may be seen in a roentgenogram of the abdomen

Periarteritis nodosa or panarteritis may cause abdominal pain although the other features of the disease are necessary for a diagnosis. The most acute abdominal pain in this disease is caused by arterial occlusion complete enough to produce mesenteric and intestinal gangrene. Small subcutaneous nodules are encountered in only about 15 to 20 per cent of cases of periarteritis nodosa

Infarction of the mesentery is usually extensive enough to require surgical treatment. Renal infarcts seldom cause pain. Infarction of the spleen if extensive may produce pain in the left upper portion of the abdomen. The most important part of the diagnosis is to recognize a source for an arterial embolus. In cases of disseminated lupus erythematosus attacks of abdominal pain are common. The characteristic cutaneous lesions affecting young adults and associated with a febrile course and leukopenia may lead the physician to consider such a disease

Trauma of major or minor significance may produce a strain rupture or hemorrhage in the rectus muscle on either or both sides

Great pain will result Cullen and Brodel have reviewed the anatomy and etiology The lower part of the rectus is most likely to be involved. The region of muscle involved may be localized Tenderness is exquisite but significantly superficial Such muscular damage often is coincident with a febrile process associated with coughing Although most frequent in the aged, this condition has been observed in young adults Frum and McLaughlin have advocated infiltration of the affected region with procaine hydrochloride as a differential diagnostic aid It should be noted, however, that such anesthetization blocks the nerve supply of the parietal peritoneum in a similar region and also the parietal region of any reflex arc It should not receive too much emphasis

Several disorders of metabolism are significant in the production of pain in the abdomen In idiopathic porphyria, the porphyrins are excreted in the urine and feces in abnormal amounts It is a familial disease occurring in two forms In congenital porphyria abdominal pain seldom occurs In acute porphyria young women are usually affected Abdominal manifestations are common and consist of cramping pain over the lower part of the abdomen associated with constipation and vomiting Distention of the abdomen and fever often follow Muscular weakness, frequently in a bulbar distribution, seldom fails to be present in some degree The patient may tell of passing red urine or urine which becomes dark when exposed to light Watson and Schwartz have described a qualitative test for porphobilinogen in the urine which is accurate for diagnosis and quickly done It is not too complicated for an average laboratory Unfortunately there is no adequate treatment of porphyria All toxic substances and drugs should be avoided and therapeutic measures should be directed toward protection of the liver

Patients in a state of thyroid crisis may have intense generalized abdominal pain with much tenderness and vomiting The restlessness, tachycardia and weakness will be severe The intravenous administration of strong solution of iodine (Lugol's solution) in isotonic saline solution will usually cause a definite improvement in a few hours

The diagnosis of abdominal pain in a state of acidosis, especially diabetic, is usually not difficult, since simple laboratory work will make the condition evident

In crises of adrenal insufficiency the shocklike state of the patient, the typical pigmentation and the rapid response to treatment with adrenal cortical extract explain the severe abdominal pain and rigidity Vomiting is often profuse

In most of the acute infectious diseases abdominal pain may be

part of the early picture. Infections involving the basal regions of the pleurae often cause pain in the upper part of the abdomen on the affected side but careful examination should avoid confusion. Diarrhea soon follows pain in a case of acute infectious gastroenteritis and the acute exanthems, especially in children, are often productive of pain and vomiting. The virus infections, such as influenza, may produce abdominal pain. Generalized muscular aching, respiratory symptoms and leukopenia help the physician to make the diagnosis. Mesenteric adenitis, frequently encountered at the removal of a normal appendix, may be due to a virus infection.

Attacks of migraine often have an abdominal component which is likely to produce more severe pain than either functional intestinal disease, such as so-called spastic colitis or an irritable bowel syndrome due either to food sensitivity or to allergic reactions. However, a patient suffering from migraine usually has some of the other stigmas, such as headache, either coincident with the abdominal pain or in previous attacks in which some relationship between the two may be clear. The abdomen is seldom rigid and sometimes not even tender in migrainous attacks.

In functional intestinal disorders of all types nervous tension frequently precedes the attack, the pain is widespread and shifting, and disability is out of proportion to the disease. In the diagnosis of specific food allergy elimination diets are of more value than tests of cutaneous sensitivity.

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THE USE OF THE NEWER SULFONAMIDES AND ANTIBIOTICS IN INTESTINAL DISEASES

J ARNOLD BARGEN

MANY drugs of the sulfonamide group have been employed in treatment of diseases of the intestinal tract. These drugs have been given by mouth, by instillation into the intestine and by subcutaneous and intravenous injections. It became apparent rather early in experience with these drugs at the Clinic that if favorable results were to be expected rather large quantities should be administered. This seems logical when the nature of the long intestinal tube is considered. Furthermore, long-continued contact of the drug with the intestinal lining and wall seemed advisable in order to inhibit or destroy the numerous bacteria constantly present in the intestine. These facts limited the choice of sulfonamide drugs to those of minimal systemic absorption and minimal toxicity.

Compounds have been developed in recent years each presumably with greater therapeutic effect in some respects and also with less toxic effect than its predecessor. These drugs were found to have variable effects in a variety of intestinal disorders. Among the conditions in which these drugs were found to have favorable effects were such diseases as the thrombo-ulcerative form of ulcerative colitis, regional ulcerative colitis, ulcerative colitis due to the virus of venereal lymphogranuloma, regional enteritis, bacillary dysentery, the intestinal infection associated with diverticulitis and the preparation of patients with intestinal neoplasms for operation as well as care of intestinal fistulas. Various drugs have advantages in various diseases and disadvantages in others. The knowledge that when one of them was found unsuitable in a given case another drug of the group was available has been of great service to patients.

STREPTOCOCCAL ULCERATIVE COLITIS

Streptococcal ulcerative colitis (thrombo-ulcerative colitis) has characteristic pathologic manifestations and hence typical proctoscopic and roentgenologic features. The lesions begin in the most distal segment of the rectum, just above the anal canal. Whether 1 inch (2.5 cm) of the lower part of the rectum or 5 feet (1.5 meters) of large intestine are involved, the entire circumference and the deeper layers of the involved segment of the wall are always affected and the mucosa is involved secondarily. Because of this com-

plete involvement of the segment affected, the granular, easily bleeding mucous membrane is characteristic of streptococcal ulcerative colitis. The disease tends to spread upward until the entire large intestine, and in the late stages of the disease, even the lower part of the ileum become involved.

Since streptococcal ulcerative colitis is primarily a disease of the intestinal wall, a characteristic roentgenologic picture is seen. The intestine becomes diffusely narrowed, haustral markings are erased and the flexures and curves become more angulated than they normally are. The result is a smooth tube. In this respect, streptococcal ulcerative colitis differs from all other forms of ulcerative intestinal disease, except perhaps regional ileitis when it is confined to the distal portion of the ileum. However, the latter condition has many features to distinguish it from streptococcal ulcerative colitis.

Streptococcal ulcerative colitis manifests itself in a variety of ways but in general the onset and clinical manifestations follow one of three general courses. When the lesions are limited to the lower segments of the large intestine, particularly the rectum and rectosigmoid, the onset of symptoms can be described as insidious. The patient may defecate normally and in addition may have two, three or many bloody, purulent rectal discharges daily. He may not have any other important systemic symptoms except that he will gradually begin to speak of not feeling well. Malaise may increase gradually as the number of rectal discharges increases and ultimately a mild form of diarrhea may develop.

In the second type of course the symptoms are severe at the onset. The disease may start rather suddenly with bloody diarrhea, low fever, gradual loss of appetite, loss of weight and all the concomitants of a moderately severe illness. All the symptoms may start in a fulminating manner almost like other serious illnesses, that is, with high fever, massive discharges of bloody material from the rectum, great prostration and rapid bodily depletion.

In the third course the patient's symptoms may remain in the insidious form for months or years and then, at the time of an infection of the upper part of the respiratory tract, some other intercurrent illness or perhaps some severe nervous strain, a sudden exacerbation of the disease and a change to a severe or even fulminating form may occur.

The hope that the sulfonamide drugs would make it possible for patients who were suffering from streptococcal ulcerative colitis to recover more quickly and with less suffering than previously has been realized in many instances. Numerous preparations have been tried and discarded because of toxicity or because they failed to have a favorable effect on the intestinal symptoms. Several sulfo-

namide derivatives less toxic and of greater effectiveness than sulfanilamide in the treatment of streptococcal ulcerative colitis are now available.

Probably the most effective drug has been azosulfamide (neoprontosil). Even with azosulfamide, however, toxic reactions with particular evidence of destruction of cellular elements in the blood have occurred. Although this untoward effect is relatively rare, yet in this disease when so much blood has been lost, further damage to the blood scarcely can be tolerated. If evidence of it is found on frequent examinations of the blood, another drug should be used. Sulfathiazole, sulfadiazine, sulfaguanidine, succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathalidine) have

TABLE 1—RESULTS OF TREATMENT OF INTESTINAL CONDITIONS WITH SULFATHALIDINE BY STREICHER

Name of Disease	Stage of Disease		Results		
	Acute	Chronic	Good	Fair	Poor
Chronic ulcerative colitis	22	58	20 acute 54 chronic	1 acute 1 chronic	1 acute 3 chronic
Amoebic colitis	4	2			4 acute 2 chronic
Bacillary dysentery		3		3 chronic	
Giardia lamblia	2	6	2 acute 6 chronic		
Paratyphoid		3		2 chronic	
Dientameba fragilis	2		2 acute		
Total number of patients	30	70	21 acute 60 chronic	1 acute 5 chronic	5 acute 5 chronic

From Streicher, M. H.: Phthalylsulfathiazole ("sulfathalidine"); clinical, chemical and bacteriologic evaluations in infectious diseases of the colon. J.A.M.A. 139 1080-1082 (Dec. 15) 1945.

been found to be effective in selected cases. Each should be administered for two weeks, stopped for a week and then given again.

Doses of from 45 to 75 grains (3 to 5 gm.) daily of sulfathiazole or sulfadiazine are well tolerated and effective, but much larger doses of sulfaguanidine are required. Sulfaguanidine is a drug of relatively low toxicity and large quantities of it can be brought into direct contact with the ulcerated intestinal surface. When it is administered orally in doses of 150 to 180 grains (10 to 12 gm.) a day concentrations in the blood will average only from 3 to 5 mg. per 100 cc.

Phthalylsulfathiazole has some advantages over the drugs previ-

ously mentioned. It is absorbed sparingly from the gastro-intestinal tract, it is rapidly excreted in the urine and in the test tube it has been found to have from two to four times the bacteriostatic activity of succinylsulfathiazole, furthermore, smaller doses are therapeutically effective. Streicher found no toxic reactions from the treatment of 100 patients with this drug. He found that patients who had the acute form of the disease made improvement comparable to that made by those who had the chronic form (Table 1). He found further that a dose of only 3 gm. divided into equal amounts and given at definite intervals in a twenty-four hour period was efficacious.

In the series of cases of chronic streptococcal ulcerative colitis in which phthalylsulfathiazole was given at the Clinic only an occasional toxic reaction was noted. One patient, a woman of forty-seven years of age, had similar reactions to sulfathiazole, succinylsulfathiazole, azosulfamide and phthalylsulfathiazole. Another, a woman of fifty-five years of age, had a severe reaction (fever, marked generalized erythematous rash and general malaise) to succinylsulfathiazole and mild similar reactions to phthalylsulfathiazole. In most cases, however, when reaction to one or another sulfonamide drug occurred, no reaction occurred to phthalylsulfathiazole. Many of the patients treated at the Clinic showed an initial satisfactory response to succinylsulfathiazole, azosulfamide or sulfathiazole but the response was not sustained. A sustained response was promptly obtained when phthalylsulfathiazole was given. In one group of cases the response to phthalylsulfathiazole was good in 70 per cent, fair in 3 per cent, slight in 3 per cent, and no apparent response occurred in 24 per cent. By response I mean reduction in the numbers of stools, decrease or disappearance of blood from the stools and relief from the concomitant symptoms of toxemia. Something should be said about the severity of the disease in these patients. In 70 per cent of the cases in which this drug was given at the Clinic the disease was severe and in 20 per cent it was in the insidious stage. In the cases in which the disease was of the so-called fulminating variety the response to the use of phthalylsulfathiazole was good in a half but in the other half no apparent response was obtained. Most of the patients who had severe symptoms made at least a satisfactory if not a good clinical improvement when phthalylsulfathiazole was administered.

Another sulfonamide compound which so far has demonstrated no toxic properties seems to have a local effect and has been used when other drugs failed or caused toxic reactions is carboxythiazole (sulfacarizole). In a series of twelve patients, all of whom had received one or all of the sulfonamides mentioned and who had

either shown only temporary or no response or who had toxic reactions from one of them including phthalylsulfathiazole, this drug was employed and at least temporary improvement occurred in every instance. The drug is relatively new and its use has not been extensive enough to allow a final conclusion to be drawn but from observations by Harris and Finland it would seem that this drug will find a definite place in treatment of chronic ulcerative colitis. The dosage is similar to that of phthalylsulfathiazole.

The administration of several of the sulfonamide drugs in a single case of colitis often has been more effective than one drug alone. Synergistic action may occur among drugs of this series or at least among some members of the series. Thus the administration of 40 to 50 grains (2.6 to 3.2 gm.) of azosulfamide and 60 to 90 grains (4 to 6 gm.) of succinylsulfathiazole or phthalylsulfathiazole has resulted in much quicker and more striking relief of symptoms than administration of either of the drugs alone.

The administration of the sulfonamide drugs in some cases has given excellent results. Maximal results will be obtained when these drugs are used early in the course of the disease. No chemotherapeutic agent can be expected to restore to normal the physiologic function of an intestine which has become contracted and deformed by disease of long standing. All that the drug can be expected to accomplish is to control symptoms due to active infection.

Penicillin was tried in the hope that it would relieve patients with the streptococcal form of ulcerative colitis. It was hoped that penicillin would be of benefit in those cases in which the sulfonamides were not effective. It seemed logical to expect that the infection in the early or active stage in which fever and other concomitant symptoms were present would be overcome. In many respects treatment with penicillin has been successful. The best results have been obtained in the acute fulminating forms in which failure has been rapid, the disease processes active and secondary fibrosis and structural changes have not been marked. It soon was found that large doses were necessary to obtain favorable change. It may develop that even larger amounts than are now being given should be administered for a period of several weeks. While the best method of administration may not have been achieved, so far the most advantageous one has been by the intramuscular route.

Streptomycin has not been given an adequate trial in streptococcal ulcerative colitis. In the few patients to whom it was administered, preliminary results were not encouraging and it is not reasonable to expect that this antibiotic agent will be suitable for the control of this disease. It may find a place in the control of some of the other forms of ulcerative colitis.

ULCERATIVE COLITIS DUE TO VIRUS OF VENEREAL LYMPHOGRANULOMA

In ulcerative colitis caused by the virus of venereal lymphogranuloma the lesions are limited to the large intestine also. The ano-rectal type of venereal lymphogranuloma which originates in the anus and distal segments of the large intestine, involves the wall of the intestine and the lymphatic structures around it. In this condition the intestine feels like a stiff tube and presents the appearance of perirectal inflammation through the proctoscope. Multiple small sinuses may penetrate from the mucous membrane to the deeper structures and a rather definite proctoscopic and roentgenologic picture results. The disease will be limited to the rectum and rectosigmoid and on proctoscopic examination normal intestine will be reached much more abruptly than in the streptococcal variety of ulcerative colitis. Almost invariably the patient will feel generally well and the complaints will be largely in reference to the local rectal condition. The diagnosis will depend largely on the history of previous venereal infection, possibly on the presence of buboes and among women commonly on the previous presence of vulval lesions. The Frei reaction will be positive. But even if these conditions exist, the diagnosis of colitis due to the virus of venereal lymphogranuloma is not tenable if characteristic lesions of the rectum do not exist.

Various sulfonamide drugs have been found helpful in relieving symptoms of the disease and in some instances they actually have affected the pathologic process favorably. After sulfanilamide has been given in the usual therapeutic doses for three or four weeks, the proctoscopic appearance of the lesions has been changed greatly. Frequently, however, the disease process has returned within a few weeks after the administration of the drug was stopped. The daily use of retention enemas, containing 60 grains (4 gm) of sulfanilamide, has resulted in complete healing of the proctitis in several months. A combination of administration of the drug by mouth and by rectum has yielded better results than either method alone. Careful determination of the level of hemoglobin and leukocyte count, as well as of concentration of the drug in the blood is important.

In some cases recession and sometimes almost complete disappearance of the rectal stricture as a result of the administration of sulfonamide drugs has been remarkable. Progressive improvement of the local lesion, as well as general improvement, such as gain of weight and euphoria, has followed the daily administration of sulfaguanidine in doses of 10 gm for a period of several months. The number of rectal discharges has decreased from between fif-

teen and twenty a day to between two and six and bleeding has stopped. The rectal stricture has been known to become softer and the adjacent rectal wall thinner and pliable.

Sulfathiazole also has been used with success. The inguinal type of venereal lymphogranuloma in particular has responded well to administration of 1.5 gm. of sulfathiazole three to five times a day for three weeks, followed by 1 gm. three to five times a day for another three weeks. In many cases proctitis and early formation of stricture have also yielded readily to such treatment. The advent of more marked stricture will of course, extend the duration of the treatment. Then the drug should be given in courses. The drug is given for two or three weeks, withheld for one week and then given again.

REGIONAL ULCERATIVE COLITIS

The cause of what is called "regional ulcerative colitis" in which the lesions usually are limited to the large intestine is not clear. Isolated segments in any part of the intestine may be involved much in the manner of regional ileitis except that the site of the disease is the large intestine. The lesion may be subacute or chronic and usually is destructive but evidence of hyperplastic changes also may be found. Commonly segments of the intestine from 6 to 12 inches (15 to 30 cm.) long are involved. The portions of the intestine distal and proximal to the lesion are entirely normal and the rectum is never involved. This segmental type of colitis ordinarily involves regions of the large intestine above the view of the sigmoidoscope. The wall of the involved segment is stiff and thickened but the involvement is not as diffuse, regular and smooth as in the streptococcal type of ulcerative colitis. Thus the roentgenologic examination is the most important objective method of establishing a diagnosis.

The lesions in the regional type of colitis usually remain localized to a segment of large intestine for months or years. Occasionally, however, they have been known to spread orad and caudad so that ultimately even the distal portion of the ileum has become involved. When the ileum is involved the difficult question of whether this and so-called regional ileitis may not be the same condition or closely related conditions always comes up. However the fact that regional ulcerative colitis usually remains localized to the large intestine whereas regional ileitis commonly spreads from the ileum proximally to involve the jejunum and distally to involve the cecum and ascending colon is evidence for the view that they are separate entities.

As in some other forms of intestinal disease, the purpose of treat

ment of regional ulcerative colitis with the sulfonamide drugs is twofold. These drugs have been employed to aid in reducing the active stage of the disease in order that resection can be undertaken more safely and as part of a medical regimen in those cases in which it is found that surgical treatment is not required. The treatment of choice has been resection of the diseased segment of bowel. However, when to operate and which patients can be restored by medical measures remain unsettled problems. With a great degree of certainty it can be said that it is unwise to explore the abdomen during the acute stage of the disease. Such complete relief of symptoms has frequently been achieved with the sulfonamide drugs that resection was later deemed unwise. I now can say that medical measures have been effective in many such cases.

Succinylsulfathiazole is the drug that is most effective in the cases of regional ulcerative colitis. When the changes in the intestinal wall are minimal, as indicated by careful roentgenologic study, a medical regimen can be instituted. From 10 to 12 gm. of the drug can be divided into equal portions so that five or six doses are given in each twenty-four hour period. This may be continued over a period of two to three weeks, then the patient should be allowed a rest of a week, after which the course is repeated. Sulfaguanidine can be given similarly. Phthalylsulfathiazole also has been tried in these cases in doses of 5 to 6 gm. a day but the results have been less successful.

When the changes in the intestinal wall are marked, with much mural damage, formation of stricture and possibly secondary polypoid change, surgical treatment may be planned at the onset. In such cases it is well to give 12 to 15 gm. of succinylsulfathiazole in divided doses daily for three to six days prior to operation.

REGIONAL ENTERITIS

Regional ileitis and intestinal tuberculosis are the two conditions which commonly start in the small intestine and tend to be confined to it for a long period. In both of them the infection is inclined to spread orad and caudad and thus ultimately parts of the large intestine and particularly the ileocecal coil are involved. The term "regional ileitis" is particularly suitable for the condition.

Regional ileitis is a subacute or chronic, destructive, exudative and proliferative, regional, inflammatory process, commonly and perhaps usually beginning in the distal portion of the ileum. In many respects the onset and clinical course are similar to those observed in the cases of regional ulcerative colitis. However, patients suffering from the latter condition are prone to be much sicker than those who have regional ileitis. The onset of regional ileitis is usu-

ally insidious but by the time medical aid is sought, well pronounced features of advanced disease are frequently apparent and the diagnosis can be established readily

As with many chronic infections of a proliferative and destructive nature the history of regional ileitis frequently begins with the complaint of fatigue, general malaise and loss of weight. At the time of onset of these symptoms or soon after, the patient will complain of a mild, usually intermittent, type of diarrhea. The stools will be loose and watery and defecation will be associated with cramps. Periods in which normal or even hard, dry stools are passed may alternate with periods of diarrhea. The history in these respects is similar to that of a patient who has intestinal tuberculosis. As a rule, however, in cases of regional ileitis, progression to the next phase is more rapid and symptoms are more severe than in cases of intestinal tuberculosis. In the former, attacks of abdominal pain soon supervene and the pain may be of the dyspeptic or obstructive type from the onset. In either event, obstructive features will soon predominate.

Regional ileitis usually has four phases. The earliest manifestation is that of an acute inflammatory process. As the terminal portion of the ileum is the most frequent initial site irritation of this portion of the intestine and its adjacent peritoneal covering produces a picture difficult to distinguish from acute appendicitis. The most common symptoms are fever of low grade, leukocytosis, nausea, vomiting and tenderness and pain in the epigastrium or right lower abdominal quadrant. At this stage of the process diarrhea and cramps are unusual.

As the disease advances, intermittent attacks of diarrhea are characteristic. The typical syndrome of mild enteritis then prevails for the patient has fever, anemia and a palpable mass in the right lower abdominal quadrant and has lost weight, his stools are loose or watery and if any pain is present, it is mild and colicky.

As the stenosing effects of the disease increase, the periods of relief which are common in the first two stages just described are shorter and occur less frequently and the third phase of the disease is reached. The symptoms typical of intestinal obstruction are superimposed on those of chronic enteritis. The attacks of diarrhea are more severe than before and are accompanied by severe abdominal cramps, borborygmus, abdominal distention or visible contracture of the coils of the small intestine proximal to the diseased segment. Malnutrition and anemia become prominent features, since the intestinal wall does not absorb much of the nourishment and fluids because of the diarrhea. Furthermore, intake may be greatly limited by persistent nausea or even vomiting.

In the fourth and final phase of the disease either acute obstruction is superimposed on the chronic condition or perforation of the wall of the intestine occurs and an abscess or fistula is formed. The fistula may communicate with an adjacent portion of the intestine, with other viscera or with the abdominal parietes. The debility occasioned by the sepsis and deprivation of nutritional elements and fluids assume great significance and these may be the terminating factors.

The use of sulfonamide compounds described under the section on regional ulcerative colitis in a general way applies to patients suffering from regional enteritis. The drugs of choice are succinyl-sulfathiazole, sulfaguanidine and phthalylsulfathiazole in the order named.

BACILLARY DYSENTERY

Bacillary dysentery may affect both small and large intestine. It has been shown recently that the lesions of bacillary dysentery are in the nature of toxic reactions mediated through a sympathetico-tonic reaction. This fact might well explain the irregular nature of the lesions and their dissemination. The various forms of true bacillary dysentery are best classified according to the nature of the infecting organism. In this part of the world, up to now the Sonne and Flexner strains have been the common ones, found either in an occasional case or in epidemics of dysentery.

In the past many forms of treatment have been employed for the control of bacillary dysentery. The sulfonamide compounds have made a distinct contribution to its control. Although sulfadiazine and sulfathiazole have been found effective in the treatment of the acute phase of dysentery, the most effective drug in my experience has been sulfaguanidine. This drug must be given in large amounts. Some physicians have advocated that 5 gm. be given every four hours for the first two days. After that the dose is decreased gradually until 2 gm. every four hours is given and this should be continued until the stools return approximately to normal, providing, of course, no untoward effects occur. Succinyl-sulfathiazole seems to have been the drug of choice for the control of the milder forms of dysentery or for the control of milder symptoms when the acute toxic phase of the disease has subsided. Large amounts should be given.

Smith, in his report of eighty-seven cases of dysentery from an army station hospital in New Guinea, described interesting results with the following three types of treatment: with sulfaguanidine alone, sulfadiazine alone, and a combination of sulfadiazine and sulfaguanidine. When sulfadiazine was used the initial dose was

4 gm then 2 gm was given every four hours for four doses and 1 gm. was given every seven hours for seven doses. In some instances administration of sulfadiazine in maintenance doses which kept the correct concentration of the drug in the blood was continued for one week. With the combination treatment of sulfadiazine and sulfaguanidine, the usual routine for administration of sulfadiazine was followed for three days and during the last day sulfaguanidine was given and continued on the fourth and fifth days of treatment. Symptomatic response in these cases was gauged by the disappearance of fever, cramps and diarrhea and the establishment of constipation or normal bowel habit. Smith also found that the remarkable relief of symptoms during treatment with sulfadiazine, or both sulfadiazine and sulfaguanidine seemed to be the response chiefly to sulfadiazine. The sickest patients were treated with sulfadiazine. Actual healing of the lesions required from three days to three weeks or even longer, depending, at least in some cases, on the time elapsing between the onset of symptoms and the institution of treatment. The objective healing of the mucosal lesions as viewed through the proctoscope was significantly faster during chemotherapy.

In an occasional instance acute bacillary dysentery may eventually in or be followed by an ulcerative form of colitis. This may occur weeks or months after the initial attack of dysentery or the acute phase of the bacillary dysentery may transform itself gradually into a chronic state. In either event a form of ulcerative colitis supervenes, although in these cases cultures of stools will almost invariably be negative. High serologic agglutination titer against one or another of the strains of *Shigella* or one of the other types of dysentery may help in establishing a diagnosis. The treatment in these cases is essentially similar to that in cases of acute bacillary dysentery except that the drugs must be given for a much longer period and other supportive measures commonly used in the treatment of patients with an ulcerative intestinal disease must also be used.

DIVERTICULITIS

In diverticulitis and other intestinal infections particularly those involving segments of the large intestine, various sulfonamide compounds have been of great help in the program of general management although they may be of secondary importance. During the active stage of diverticulitis when much swelling and tenderness are present the administration of succinylsulfathiazole or phthalylsulfathiazole in suitable amounts has materially shortened the attack of diverticulitis. In cases in which operation is necessary adminis-

tration of one of these drugs will not in any sense replace the usual surgical treatment but it may allay the acute infectious and perforative stage of the condition so that operation can be undertaken much more safely. In other cases an attack of diverticulitis may subside so completely that surgical treatment frequently becomes unnecessary or even inadvisable and these sulfonamides have helped to bring about this favorable state of affairs.

PREOPERATIVE USE OF SULFONAMIDES IN SEVERAL INTESTINAL LESIONS INCLUDING ABDOMINAL FISTULAS

The use of sulfonamide compounds in the last several years as part of the preoperative program in the treatment of intestinal lesions is valuable. It is obvious that surgical treatment of the intestine has definitely been made safer. At the Clinic we have been administering succinylsulfathiazole or phthalylsulfathiazole as a routine part of the preoperative program of management for nearly four years. Unless obstruction, the patient's general condition, or toxicity of the drug contraindicate its use we have given orally 300 grains (19.4 gm) of succinylsulfathiazole in divided doses the first day of the preoperative period and 180 grains (11.7 gm) on the next three days prior to operation. Gradually phthalylsulfathiazole has come to replace succinylsulfathiazole in selected cases and approximately 150 grains (9.7 gm) is given on the first day and 90 grains (6 gm) on the subsequent three days of the preoperative period has been given. In cases of fistula or cases in which ileostomy or subsequent closure or resection of the large intestine is indicated the instillation of one of these drugs into the intestine for several days prior to operation has been practiced.

The best results from the use of these drugs have been achieved in cases of neoplastic intestinal lesions. The routine of administration of the sulfonamides previously mentioned together with other measures of preoperative care has resulted in a remarkable reduction in mortality following intestinal operation.

SUMMARY

In various infections and other conditions and lesions occurring in the intestine patients have derived benefit from the use of the newer sulfonamides. These drugs have been administered by mouth and through intestinal fistulous openings. Their effect is largely local. Systemic absorption is minimal and so toxic effects hardly present a danger in their use. Successive drugs developed for treatment of intestinal condition in general have been less toxic or more effective therapeutically or both than the earlier sulfonamides. The

antibiotics so far have not had adequate trial in treatment of intestinal conditions. However, penicillin has found a definite place in the treatment of the streptococcal form of ulcerative colitis. It is reasonable to expect that streptomycin might also find a useful place in the treatment of some of the other intestinal infections.

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THE USE OF VARIOUS KINDS OF INSULIN

RANDALL G SPRAGUE

In the majority of cases of diabetes the disease is relatively mild and the problems of everyday therapy do not offer serious difficulties. In approximately a half of all cases glycosuria is readily controlled without insulin, and in a considerable proportion of cases in which insulin is required, there is sufficient latitude in dosage and program of administration so that serious problems involving insulin reactions and excessive glycosuria are readily avoided. Difficult therapeutic problems are fortunately limited to a relatively small group of patients having severe diabetes. Nevertheless, it must be borne in mind that insulin is a powerful two-edged weapon which must be employed with some degree of skill and care in all cases in which its use is required. The type of insulin employed and the program of administration must be adapted to the individual case if optimal results are to be obtained and difficulties with insulin reactions and poor control of glycosuria are to be prevented.

AIMS OF TREATMENT

The final aim of treatment of diabetes is the maintenance of health and vigor for a normal span of life. This implies avoidance of acute complications, such as insulin reactions and episodes of ketosis, as well as the chronic degenerative complications of the disease. Opinions differ in some details concerning the best means of achieving these aims. While practically everyone is agreed that diet and insulin are the cornerstones of treatment there is a good deal of variation of opinion among different physicians and institutions with respect to details of diet and insulin therapy and the degree of control of glycosuria which is considered desirable. Often there is not a corresponding variation in the therapeutic results which are obtained. The discussion of the use of insulin which follows is based on methods which have usually proved effective in the Clinic. Only the treatment of uncomplicated diabetes will be considered.

At the present time, it seems reasonable to believe that the most desirable treatment is that which maintains optimal nutrition and reduces the excretion of glucose in the urine to the lowest possible minimum consistent with a livable program of treatment and the avoidance of insulin reactions. Precise control of the level of the

blood sugar, which in some cases can be achieved only by bizarre adjustments of the diet and frequent injections of insulin, and in other cases cannot be achieved at all, probably does not offer any additional advantage. With the passage of years there is a growing body of evidence that even the most precise control of diabetes is not a crucial factor in the prevention of degenerative complications. Their pathogenesis and prevention still loom large among the unsolved problems of diabetes.

INDICATIONS FOR THE USE OF INSULIN IN THE TREATMENT OF DIABETES

Insulin therapy is indicated in practically all cases in which glycosuria is not, or obviously will not be, entirely controlled when the patient adheres to a weighed or carefully estimated diet which is palatable and nutritionally adequate. In only rare instances is it justifiable to resort to rigid restriction of the carbohydrate content of the diet in order to avoid the use of insulin. This is occasionally necessary among elderly patients who by reason of debility, poor vision or some other insurmountable difficulty are unable to administer insulin to themselves or to have it administered to them by others. Even in cases of mild diabetes in which ordinarily complete freedom from glycosuria is maintained by dietary means alone, insulin may be necessary in periods when complicating illness temporarily intensifies the diabetes.

It is possible to anticipate with considerable accuracy the need for insulin in many cases of newly discovered diabetes. Such cases include those in which the patients are children, adolescents or lean adults less than forty-five years of age. In such cases there is a reasonable certainty that the disease will ultimately prove to be of sufficient severity to make the use of insulin obligatory, and it is wise to begin its administration at the outset of treatment and thereby indoctrinate the patient in its use at a time when he is under close observation.

Other cases in which insulin therapy is best initiated at the time of discovery of diabetes are those in which there are severe hyperglycemia and glycosuria at the outset, even though the disease can be predicted to be fundamentally mild. The patients in this group as a rule are obese young adults, the senescent or the senile. The use of insulin, though only temporary, in such cases has the virtue of shortening the period necessary for control of glycosuria. Furthermore, in many cases tolerance will improve greatly with control of glycosuria and the dose of insulin can be reduced and eventually discontinued.

THE PHYSIOLOGIC PROBLEM INVOLVED IN THE TREATMENT OF DIABETES WITH INSULIN

The normal physiologic mechanisms involved in the secretion of insulin by the pancreas are not entirely understood and, even if they were understood, they would not be easy to imitate. Nevertheless, it is helpful to have in mind some physiologic basis for thinking of the problem involved in the treatment of diabetes with insulin. The theoretical aim in administering insulin to the patient who has diabetes is to supplement his endogenous production of insulin in such a way as to approximate the normal mechanisms of secretion of insulin by the pancreas. Indirect evidence suggests that there are normally (1) a continuous slow secretion of insulin during fasting which serves to prevent excessive catabolism of body protein and fat and maintain the blood sugar at a normal level against the various factors which tend to elevate it, and (2) an augmented secretion following the ingestion of food, which prevents the excretion of more than minute amounts of glucose in the urine. Obviously in treating human diabetes there are no practical means of achieving an exact imitation of these mechanisms but the physician is usually able, by skillful employment of quick and slow acting types of insulin in proper doses, to attain a satisfactory approximation of the normal processes.

TYPES OF INSULIN AND THEIR ACTION

Commercial insulin is available in several different forms and other forms are receiving clinical trial. This discussion will be limited to those forms of insulin which are now generally available and to combinations of these.

Soluble Insulin—This term is used to include both regular insulin and solution of zinc insulin crystals. The effects of regular and crystalline insulin are so nearly alike as to be indistinguishable clinically.

Since soluble insulin is in aqueous solution, it is absorbed rapidly following subcutaneous injection. Its effects, therefore, are characterized by prompt onset, rapid lowering of the blood sugar and an early fading of effect. After the subcutaneous injection of a moderate sized dose (in the neighborhood of 20 units) the blood sugar begins to fall almost immediately reaches its lowest level in perhaps three hours and then begins to rise so that about six hours after injection it is back to its starting level and all insulin action so far as can be determined by the level of the blood sugar is expended. Because of its short lived, intense action, a single injection of soluble insulin will not maintain control of severe diabetes.

for more than a few hours. Consequently, three or four injections in each twenty-four hours may be necessary for precise control of severe diabetes.

Protamine Zinc Insulin—At the pH of the tissue fluids protamine zinc insulin is a fine white precipitate of low solubility. When it is injected subcutaneously, insulin is released from its combina-

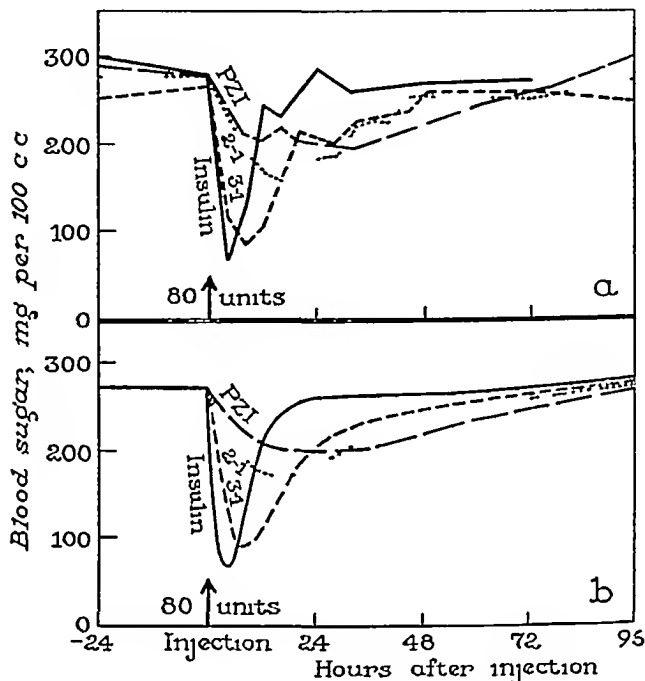


Fig 122—Average blood sugar curves following injection of equal doses of four different preparations of protamine zinc insulin and soluble insulin, illustrating gradation of promptness, intensity and duration of action with increasing proportions of soluble insulin. PZI refers to protamine zinc insulin alone, 2-1 refers to a mixture containing 2 parts of soluble insulin to 1 part of protamine zinc insulin, 3-1 refers to a mixture containing 3 parts of soluble insulin to 1 part of protamine zinc insulin, and *Insulin* refers to soluble insulin alone. Each subject received an almost identical feeding every four hours, day and night, during the test periods. *a*, Actual blood sugar curves, *b*, diagrammatic representation of curves shown in *a*, arbitrarily smoothed to discount minor irregularities considered not to be due to insulin. (Redrawn from Colwell, Izzo and Stryker,² reprinted from Sprague⁴)

tion with protamine very slowly. As a consequence, the action of protamine zinc insulin is slow in onset and relatively weak but prolonged. A single injection of 20 units exerts a continuous depressing effect on the blood sugar for twenty-four to thirty-six hours, while larger doses act for longer periods. This type of insulin does not provide sufficient intensity of insulin action in cases

of severe diabetes to prevent the excretion of considerable amounts of glucose following the ingestion of food, and its prolonged effects may cause hypoglycemia during the fasting hours of the night

Mixtures of Soluble and Protamine Zinc Insulin—Protamine zinc insulin contains enough protamine to precipitate considerable amounts of added soluble insulin and thereby abolish the quick effect of the latter. Consequently, mixtures of small amounts of soluble insulin and large amounts of protamine zinc insulin have an action which is virtually indistinguishable from that of protamine zinc insulin alone. Thanks largely to the work of Colwell and his colleagues,² the action and clinical usefulness of mixtures of the two types of insulin have been greatly clarified.⁶ They showed that definite intermediate effects, in terms of promptness, intensity and duration are not obtained until the mixture contains at least as much soluble insulin as protamine zinc insulin. By varying the proportions of soluble to protamine zinc insulin any effect intermediate between those of the two kinds of insulin alone can be obtained. When the proportion of soluble insulin in the mixture is increased above a ratio of about 1:1, promptness and intensity of action are augmented, while duration of action is diminished (Fig. 122).

Globin Insulin—The action of this preparation is intermediate between that of soluble insulin and that of protamine zinc insulin in promptness, intensity and duration. Doses of moderate size are said by some observers to be active for approximately twenty-four hours. Globin insulin is a clear solution. Colwell¹ has suggested that this supposed advantage may have been overemphasized. The homogeneity of the preparation is accomplished by acidification and, since the globin insulin compound is precipitated from solution on alkalization by the tissue fluids, there may be some variability of action due to differences in degree of precipitation from one injection to the next.

PROGRAMS OF ADMINISTRATION OF INSULIN

In most cases of diabetes it is possible to achieve complete, or nearly complete, freedom from glycosuria by several different programs of administration of insulin. It is desirable to use the simplest program that will achieve the desired end with the least possible danger of insulin reactions. There is nothing to be gained by imposing a program of three or four doses of soluble insulin daily on the adult patient who has relatively mild diabetes, when a single small dose of protamine zinc insulin taken in the morning before

* For a discussion of another special modification of protamine zinc insulin which combines both prompt and prolonged effects but which is not generally available the reader is referred to the work of MacBryde and Roberts.

breakfast would suffice to keep his urine free of sugar throughout the twenty-four hours. On the other hand, it is not wise, in a search for simplicity, to prescribe a single large morning dose of protamine zinc insulin for a juvenile patient who has severe diabetes and a high requirement for insulin. On such a program he is likely to encounter two kinds of trouble, namely, intense glycosuria during the day, when food is being ingested, and insulin reactions at night as a consequence of continued insulin action while fasting. Neither is it desirable to resort to bizarre dietary programs in an effort to make a simple insulin program effective, for this merely substitutes one inconvenience for another. Rather, a suitable diet should be prescribed and the program of administration of insulin adapted to the individual patient's needs.

Frequent tests of the urine for sugar are the guide for adjustment of the doses of insulin. In the early treatment of newly developed diabetes, tests are performed four times daily—in the morning before breakfast, in the forenoon before lunch, in the late afternoon and at bedtime. In order to provide accurate information concerning the state of the diabetes at the time when the test is made, the urine should have been recently secreted by the kidneys. The patient is, therefore, instructed to empty the bladder about thirty minutes before collecting the specimen for testing. After preliminary regulation has been accomplished, the patient is instructed to test the urine one, two, three or four times daily, depending on the severity of the diabetes and the desired precision of control. As a rule, patients who have diabetes of moderate severity can keep adequately informed of their progress by testing twice daily, in the early morning and late afternoon.

Since the aim of treatment is to maintain the urine as nearly sugar-free as is compatible with the avoidance of insulin reactions, determinations of the blood sugar are not of any greater service than tests of the urine as a guide to treatment. Unless blood sugar tests are done at intervals throughout the day, which is not feasible as a routine method of following progress, they are distinctly less valuable than fractional tests of the urine. In occasional difficult cases during the period of regulation in the hospital or clinic, estimations of blood sugar at various times of the day may be helpful in finding the solution to individual problems of treatment.

Treatment with Soluble Insulin Alone—There still remain a few cases in which, for one reason or another, diabetes is most effectively treated with soluble insulin alone. For the most part, these patients are included in the following groups:

1. Those having diabetes of moderate severity who have used two or three doses of soluble insulin daily for years, who have done

well with respect to control of glycosuria while avoiding insulin reactions and who are not seriously inconvenienced by two or three hypodermic injections daily

2 Those having diabetes of moderate severity which is not satisfactorily controlled with a single morning dose of protamine zinc insulin and who are not able to master the intricacies of a combined dose of protamine zinc insulin and soluble insulin taken in one syringe. For such patients, soluble insulin given before breakfast and before supper combines the virtues of relative simplicity and effectiveness

3 A small number of patients having severe "brittle" diabetes who have difficulty with insulin reactions and excessive glycosuria on any program involving the use of protamine zinc insulin either alone or in combination with soluble insulin. These are the patients who are most difficult to treat, regardless of what program is used. Some, but not all, of them are more readily managed with three or four doses of soluble insulin daily than they are with any program utilizing protamine zinc insulin. The largest dose is administered before breakfast, a dose of about half this size is given before supper and a small dose (4 to 12 units) is given at bedtime. Usually a dose before lunch is not necessary since the morning dose can be made sufficiently large to prevent excessive glycosuria in the forenoon and afternoon without danger of serious reactions. The small dose at bedtime serves to prevent the escape from control which often occurs among patients having severe diabetes who do not take any insulin during the twelve or fourteen hour period between supper in the evening and breakfast the following morning.

Adjustment of the doses of soluble insulin to the needs of the patient is usually not difficult if a few simple principles are kept in mind. Reactions are an indication for reduction of the preceding dose unless the reaction is due to a sporadic increase of physical activity or decrease of food intake. Persistent excessive glycosuria calls for an increase of dose. If it occurs during the forenoon or afternoon the morning dose should be increased. If it occurs between supper and midnight, the evening dose should be increased. If it occurs between midnight and morning, a small dose at bedtime usually should be added. There is an accumulation of effect of multiple doses which are spaced no more than eight hours apart. Because of this, if it is necessary to give insulin before each meal the noonday dose can be considerably smaller than the morning dose for its effect is reinforced by the morning dose. Likewise a noonday dose reinforces the dose which is given before supper.

Treatment with Protamine Zinc Insulin Alone.—It is now obvious that when used alone protamine zinc insulin does not have as

wide an application as was once hoped. It gives the best results among patients who have diabetes of relatively mild degree, particularly adults whose daily insulin requirement is 20 units or less. In these patients, the disease is also readily controlled with two doses of soluble insulin, but protamine zinc insulin has the advantage of being effective in keeping the urine free of sugar with minimal danger of hypoglycemic reactions, when given as a single small dose in the morning before breakfast. The stable behavior of the diabetes in this group of patients makes frequent adjustments of the dose of insulin unnecessary.*

Among patients having more severe degrees of diabetes, most of whom are in the juvenile, adolescent or lean adult group, attempts to control glycosuria with a single large dose of protamine zinc insulin usually meet with failure and the hazard of prolonged nocturnal hypoglycemic reactions may be considerable. In these cases, the disease is likely to be of such severity as to require a relatively intense insulin action during the day when food is being ingested. If sufficient protamine zinc insulin is injected in the morning to supply the requisite intensity of insulin action during the day, there is excessive insulin action during the hours of fasting through the night, resulting in hypoglycemic reactions. A common sequence of events in such cases is excessive glycosuria during the day and evening, clearing by midnight or shortly thereafter, and hypoglycemia in the early hours of the morning. Such episodes of hypoglycemia may go unrecognized. Since they are likely to cause a further depression of carbohydrate tolerance during the succeeding day, the patient or the physician may be led to increase the dose of protamine zinc insulin, which serves only to augment the difficulties. Reduction of the total dose of insulin and a change to an appropriate combination of protamine zinc insulin and soluble insulin may solve the predicament.

Treatment with Combinations of Protamine Zinc Insulin and Soluble Insulin—Although such mixtures do not solve all the problems of treatment of severe diabetes, they at present provide the most effective and rational form of insulin for use in the majority of such cases. The combined dose is administered in one syringe in the morning before breakfast. The strong effects of soluble insulin prevent excessive glycosuria during the day when food is being ingested, and the prolonged slow action of protamine zinc

* Not all of the patients in the senescent and senile groups have mild, stable diabetes. In a few of them the disease has all the characteristics of "brittle" juvenile diabetes. It then presents a difficult therapeutic problem, which is not adequately coped with by a single morning dose of protamine zinc insulin.

insulin prevents escape from control overnight. Necessary flexibility is provided by the use of extemporaneous rather than fixed mixtures of the two types of insulin * Mixtures containing two to three times as much soluble insulin as protamine zinc insulin are the most suitable in the treatment of severe diabetes In eighty seven of 100 patients who were recently treated with mixtures the ratio of soluble insulin to protamine zinc insulin was between 2 1 and 3 1

In a new case in which there is intense glycosuria but it is uncomplicated by severe acidosis, the size of the initial mixed dose must be determined by clinical judgment and an estimate of the severity of the disease If the diabetes is anticipated to be relatively mild, the starting dose may be of the order of 6 units of protamine zinc insulin and 12 units of soluble insulin If the diabetes is of greater severity, the dose may be of the order of 12 units of protamine zinc insulin and 24 units or more of soluble insulin Rarely should the initial total dose exceed 60 units Young children usually respond to smaller doses than adults In the absence of ketonuria, increases of dose should be made cautiously during the first few days of treatment, for the full effects of the starting dose may not be apparent for several days

Many patients do not remain under continuous observation with diet and activity fully controlled for a long enough period to become established on a "standard" program which will not require further alteration. Other patients have such great fluctuations in requirement for insulin from time to time that it is never possible to establish a standard program Consequently, it is important that the physician impart to his patients a clear understanding of the principles of adjustment of dosage so that they may continuously avoid excessive glycosuria on the one hand and hypoglycemic reactions on the other Unfortunately, in cases of severe diabetes such nicety of adjustment is not always easy to accomplish, even under optimal conditions

Whatever the initial dose of insulin subsequent adjustments are

The use of extemporaneous mixtures of protamine zinc insulin and soluble insulin in one syringe calls for precautions to prevent the introduction of one kind of insulin into the other bottle An appropriate volume of air is first injected into the bottle of protamine zinc insulin and the needle is withdrawn without permitting any insulin to enter the syringe Then the desired dose of soluble insulin is drawn into the syringe in the usual manner After this the needle is again inserted into the bottle of protamine zinc insulin and the desired dose is allowed to flow into the syringe, overlying the soluble insulin which is already there The two kinds of insulin are mixed by drawing a small bubble of air into the syringe inverting the syringe several times and then expelling the bubble.

made on the basis of fractional tests of the urine. During a preliminary period of observation in the hospital or clinic, the urine is tested four times daily. Once reasonable control has been established, adjustments of the doses of the two kinds of insulin can be made on the basis of two daily tests. The test of a fresh specimen voided in the morning before breakfast is a reasonably good criterion of the adequacy of the dose of protamine zinc insulin. The dose is adjusted so that there will be no nocturnal reactions and no more than traces of sugar in this specimen. Likewise, the test of a fresh specimen voided late in the afternoon before supper serves as an index of the adequacy of the dose of soluble insulin. This dose is adjusted so that there will be few or no insulin reactions during the day and no more than traces of sugar in this specimen.

In cases of severe diabetes, once preliminary regulation has been completed and tolerance has become stabilized, it is not advisable to make frequent changes in the doses of the two kinds of insulin, since there may be many factors other than insulin which determine transient fluctuations of glycosuria. Among these are variations of physical activity, emotional disturbances, irregularities of rate of absorption of insulin and variations of food intake and physical activity. A sound principle is to find a dose of insulin which provides adequate control on most days and adhere to it until there is good reason to make a change.

When the dose of insulin is altered, the magnitude of the change should depend on several factors. As a rule, the larger the dose, the larger the change should be. For most adult patients requiring up to 40 units daily, changes in steps of 4 units are advisable. Very large doses can be raised or lowered 6 or 8 or more units at a time. Some patients, particularly children, are so sensitive to small changes that alterations of 2 units at a time are sufficient.

In an appreciable number of cases of severe diabetes glycosuria is not adequately controlled and insulin reactions are not avoided throughout the twenty-four hours by the use of a single combined dose of protamine zinc insulin and soluble insulin. In such cases it is advisable to add a small dose of soluble insulin before supper. Usually it need not exceed 10 or 12 units. When this program is employed, adjustments of dose are made chiefly in the soluble insulin taken in the morning and evening. Once control has been established, the dose of protamine zinc insulin requires little or no alteration. The afternoon test serves as an index of the adequacy of the morning dose of soluble insulin, and the morning test as an index of the adequacy of the evening dose of soluble insulin.

Treatment with Globin Insulin.—Because globin insulin combines both prompt and prolonged actions, it is an effective form of

therapy in many cases of moderate severity when it is administered in a single dose in the morning before breakfast. In such cases it has definite advantages over protamine zinc insulin alone but not over appropriate mixtures of protamine zinc insulin and soluble insulin. There is sufficient residual insulin action through the night to prevent excessive glycosuria and azoturia if the diabetes is not too severe and hypoglycemic reactions in the night are uncommon.

In cases of more severe diabetes of the "juvenile" type, it may be found that globin insulin exhausts so much of its activity in the first twelve hours after injection that insufficient activity remains to control the diabetes through the night. Therefore, better results are sometimes obtained in such cases with two doses daily administered in the morning before breakfast and in the evening before supper. The morning dose as a rule is two to four times the size of the evening dose.

The claim has been made that allergic reactions as the result of administration of globin insulin are extremely rare. So rarely do such reactions constitute a major problem with any type of insulin that in most cases this feature alone need not be given serious consideration in deciding which insulin to employ.

SUMMARY

Diabetic patients differ greatly in their response to treatment with insulin. In some cases diabetes is readily controlled, while in other cases it is relatively refractory to treatment. The reasons for variability between cases are not understood but it may be that different etiologic factors, different forms of the disease, or perhaps only differences in intensity of the disease are involved. Regardless of the causes of variability the therapeutic measures used and particularly the manner in which insulin is employed, must be adapted to the individual case. At present it seems that a therapeutic regimen which, with the least inconvenience, reduces the excretion of glucose in the urine to the lowest possible minimum compatible with the avoidance of insulin reactions, and maintains normal nutrition is the most desirable from all points of view. Programs of administration of insulin utilizing soluble insulin alone, protamine zinc insulin alone, mixtures of soluble insulin and protamine zinc insulin, or globin insulin alone are applicable to different types of patients.

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AN APPRAISAL OF RADIUM THERAPY

ROBERT E. FRICKE

In considering the value of radium treatment in modern therapeutics one must bear in mind that this form of therapy is a distinct specialty. In fact, it is a highly specialized branch of medical therapeutics. At the present time the most essential use of radium is in combating many forms of malignant disease often in conjunction with surgical and with roentgen treatment. Radium is an exceedingly powerful source of energy. One is in reality using atomic or nuclear energy, now so familiar from its destructive use in the atomic bomb. It is fitting that this most tremendous energy known to man is employed against his most relentless and merciless illness. Physicians employing radium are the first to make constructive use of atomic energy.

DEVELOPMENT

Radium therapy is a mere infant in our medical armamentarium. Therapy by surgical means or by drugs has existed for centuries. The announcement of the discovery of the new element radium, made in 1898, followed by two years Roentgen's sensational work. Becquerel's burn of 1901 and Pierre Curie's test of his own skin on exposure to radium showed that the new element had definite effects on tissue. In France, empirical treatment of chronic ulcerative lesions of the skin was begun; encouraging results expanded efforts of French physicians. Their reports speeded work in other countries. In 1905 the first radium treatment of cancer of the cervix was reported by Abbe.

By 1907 Dominici pointed out the advantage of more homogeneous irradiation by means of heavy filtration; the employment of heavy metal around the radium stopped the more caustic, softer rays and permitted a heavier dose in the deep tissues. Dominici was a physician in Paris who was also an eminent physiologist and hematologist and worked with Wickham and Degrais, studying the biologic effects of irradiation. Dominici's work revolutionized radium therapy and the more scientific application of radium began with this innovation.^{3, 17}

The development of radium therapy from 1907 on has been phenomenal. No branch of medicine has been so intensively and advantageously studied. This was mainly because of the simultaneous developments in physics, surgical pathology, electrosurgery,

research on the biologic effects of irradiation and other branches of cancer therapy. Early workers in radiology accelerated the development of the new science with their enthusiasm and industry. Details of early work can be found in "The science of radiology," a book prepared for the First American Congress of Radiology held in 1933.¹⁰

Many changes in radium therapy have occurred during the twenty-five years that it has been my privilege to work with radium and roentgen rays. Fortunately, my apprenticeship consisted of several years spent with the late Howard A. Kelly and with Curtis F. Burnam, of Baltimore, pioneers who first brought the value of radium therapy to the attention of the American medical profession through their admirable papers presented at annual meetings of the American Medical Association in 1914 and 1915.^{11, 12}

In the early years, enthusiasm aroused by excellent results in certain diseases tempted radium therapists to treat almost every ailment. I should hesitate now to name many of the diseases treated hopefully at that time.

At present, radium therapy has attained a measure of maturity. Indications and contraindications are more generally understood than in earlier days, the diseases which are radiosensitive are now known and treated intensively.

Much of the astonishing progress of irradiation therapy is due to the free interchange of ideas and explanation of new techniques afforded by annual meetings of the national societies of radiologists, such as the American Radium Society, the American Roentgen Ray Society, the Radiological Society of North America and the Radiologic Sections of the American Medical Association.⁵ These contributions to improved therapy are published in the journals of these societies.

DISADVANTAGES AND OBSTACLES

The physician specializing in radium therapy has certain discouraging factors to face. These can be overcome but they retard the development and steady improvement of radium therapy.

One factor is the erroneous concept of expense, the idea that radium is a fabulously expensive element and that every other form of treatment should be attempted first. This notion arises from the exorbitant cost of the element in the early years of the present century. The history of radium production is one of monopoly in one country after another. Shortly after the discovery of the usefulness of radium, American physicians had to buy the purified product from factories abroad at approximately \$135,000 a gram.

or \$135 a milligram, though often the crude ore came originally from this country. After the technic of refining the ore was developed in this country about 1913 the United States supplied most of the world's radium at \$120 a milligram and enjoyed this monopoly for practically a decade. During the first World War, the price was \$110 and later \$100 a milligram. Then ore rich in radium content was discovered in the Belgian Congo and Belgium was able to produce profitably at \$70 a milligram thus stopping all American production.⁶ For many years Belgium supplied the needs of the world. In 1930, the LaBine brothers' sensational discovery on the shores of Great Bear Lake in the Canadian Northwest began to produce. Belgium dropped the price to \$50 a milligram in 1932 and finally in 1936 to \$25 a milligram where it still stands for radium of Canadian and Belgian origin.¹³

This present price is not excessive. Radium is used for one patient after another. The disintegration of radium is gradual in relation to the length of human life—that is, 1 per cent every quarter of a century. In 1 690 years only half of any supply will have vanished, in another 1 690 years half the remainder and so on. Thus a tube of radium, unless lost, can serve for centuries. Considering the tons of chemicals and the months of time necessary for the purification process and the intrinsic value of the product in medical practice \$25 a milligram is a very reasonable price. Moreover, commercial agencies rent radium in any amount and prepare it to order.

Another obstacle, besides the erroneous idea of unreasonable expense is the reasoning that when radium treatment is applied to patients who have extensive malignant lesions, the treatment is responsible when death occurs. Because of the remarkable palliation achieved by treatment, physicians apply radium in cases of hopeless advanced cancer, knowing that cure is out of the question and that life may not be prolonged but that easing of pain and lessening of discharges are worth the attempt. Before the advent of irradiation therapy hypodermic injections of morphine were about the only treatment known for these hopeless patients although relief of pain has been achieved by section or injection of nerve trunks and the use of colloidal gold has its advocates.¹⁶

Still another obstacle in some cases is lack of experience and skill on the part of the radium therapist. Patients who do have faith in radium therapy regard radium as a form of magic, which can achieve miracles in the hands of anyone. Rental of radium by the inexperienced physician is a simple transaction and tremendous harm may result from injudicious treatment. Surgeons who lack experience in therapeutic radiology may borrow or rent radium accepting the responsibility for the treatment that is begun when

they place it in the course of an operation Poor results impede the advancement of radium therapy As radium is a tremendously potent physical agent, it should be rented or supplied only to diplomates of the American Board of Radiology

ADVANTAGES AND USEFULNESS

There is no question that the rays and particles given off by radium and its decay products can kill cancer cells Biopsies taken following treatment at various intervals have shown the effect of the radiations on the malignant cell and on the cancer bed Of course,



Fig 123—Biopsy specimen of carcinoma of the cervix, before treatment for squamous cell epithelioma, grade 2 (Broders' method) When the patient died two years later following appendectomy, no residual carcinoma was found at necropsy ($\times 150$)

this atomic energy emitted by radium can destroy all tissue if im properly used But the rays are more selective than the surgeon's knife, irradiation has lethal effect on cancer cells at dosages which do not permanently harm normal cells (figs 123 and 124)

This ability to destroy cancer is an important advance in medicine With longer life expectancy, cancer afflicts more people than in earlier periods and is second only to heart disease in the United States mortality tables Recently the American Cancer Society stated that 600,000 persons in America have cancer at present, that one of every eight persons now living will die eventually of cancer and

that cancer kills 60 per cent more persons than all the infectious diseases combined.²

The tremendous scope of the cancer problem has made it a public health concern. In 1937 Congress passed the National Cancer Institute Act, creating the National Cancer Institute under the United States Public Health Service, and purchased 95 gm of radium for cancer therapy and research.¹⁴ This large store of radium is loaned to approved institutions for cancer therapy, preferably for patients in the lower income groups. Wisely, only radiologists possessing qualifications equivalent to those established by the American Board of Radiology may use this government radium.

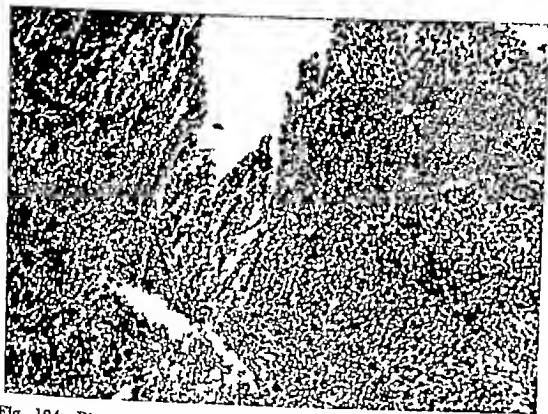


Fig 124—Biopsy specimen of carcinoma of the cervix before treatment, squamous cell epithelioma, grade 3. When the patient died six years later of hepatic disease, no residual carcinoma was found, although an inflammatory mass was present involving the right ovary ($\times 100$).

Cancer can be successfully arrested by radium, roentgen rays or surgical treatment, or by a combination of these methods, but this is possible only when the cancer is diagnosed early while it is still a local disease and when it is in an accessible location. Hence, radium has its greatest usefulness in treatment of cancers of the genital tract in women, the urinary bladder, the rectum, the oral cavity, the pharynx and the skin. For many years of all the patients treated for malignant disease with radium at the Mayo Clinic, approximately 45 per cent each year were referred from the Sections on Gynecology.⁷ Many serious cancers heal and the patients remain

well over a period of many years. Each year in our section on radium therapy we have examined returning patients who had no evidence of cancer at the time of their return but had been treated for an otherwise fatal disease ten, fifteen or twenty years previously. I have known one pelvic cancer to recur suddenly after the patient



Fig 125 —Before radium treatment, stage 4, carcinoma of the cervix. Left pyelocaliectasis and left ureterectasis.

had enjoyed twenty-three years of good health, it is impossible to say whether this was a true recurrence or a new cancer in a person susceptible to malignant lesions.

Another advantage of radium is that it is an extremely flexible physical agent. Used either as the element or as radon, which is the

first decay product it can be placed in very small applicators and introduced into body openings or sinus tracts, again as needles containing the element or seeds containing radon it may be inserted directly into tumors. Also, radium in tubes can be placed on the skin or at fixed distances from the skin to treat tumors deep in the



Fig. 126—Same patient as in figure 125 four months after radium treatment
Excretory urogram grossly negative.

body. To obtain radon the salt of radium is dissolved in water. The gas radon forms daily and is purified and collected. Being a gas, it can be sealed in smaller containers than the element itself and if it is transported to other hospitals for use, breakage or loss is not a permanent loss as the element itself is in solution and con

tinually producing more radon. As radon disintegrates rapidly—a sixth of its value vanishes daily—calculations have to be made in figuring dosage which are not necessary when the more stable radium salt is used. Thus radium in small containers can be placed in the midst of, or in contact with, malignant tissue and the rays



Fig 127—Before radium treatment, stage 4, carcinoma of the cervix. Right hydronephrosis, nonfunctioning left kidney.

do not have to traverse normal tissue to reach the disease, as is usually necessary with roentgen rays. In many instances, both agents are used, radium internally combined with roentgen rays externally.

Another advantage is that of exact dosage. The energy given off

during the disintegration of radium and its decay products is produced at a constant rate, which cannot be changed by ordinary chemical or physical measures. Given all the treatment factors dosages can be duplicated anywhere without the constant checking necessary to correct variations, as in x-ray and other electric apparatus.



Fig 128—Same patient as in figure 127 three months after radium treatment. Hydronephrosis gone on right, left kidney functioning

PALLIATION OF MALIGNANT LESIONS

Cancer is of course a fatal disease unless diagnosed and treated properly while still a localized lesion. Once spread throughout the body by metastasis arrest for any length of time is unknown. In considering radium therapy it is difficult to understand the emphasis

placed on cure and the lack of appreciation of palliation. Even if life is not prolonged, the relief of pain and cessation of hemorrhage and noxious discharges are well worth while. In the field of general medicine, advanced heart disease, arteriosclerosis, diabetes mellitus and hypertension are not curable but effectual palliation is secured by proper medication and a different regimen of life.

Even the uremia which ends the picture in cases of cancer of the cervix from compression of the ureters by extension of the growth to the broad ligaments can often be postponed by radium treatment (figs 125, 126, 127 and 128).

BENIGN DISEASE

While the treatment of malignant lesions is the most important contribution of radium therapy, many painful or troublesome benign tumors and lesions are curable by radium therapy. Menorrhagia of the menopause, with or without small fibroids, is safely and effectively treated with a menopausal dose of radium after curettage to exclude the possibility of cancer. In many thousands of cases hysterectomy has been avoided by this simple and safe form of treatment.

Several types of birthmarks in infants respond readily to radium and heal with smaller scars than following other forms of treatment.

Lymphangiomas respond slowly to repeated treatment, as do actinomycosis and tuberculous adenitis. Acute inflammatory lesions also subside with treatment.⁴

Hypertrophied lymphoid tissue in the nasopharynx, causing repeated colds, sore throats and often partial deafness, is cleared up readily by radium treatment.^{8, 9} Radium treatment appears to delay or prevent recurrence of nasal polyps following polypectomy.

In 1944 in the Mayo Clinic more patients were treated with radium for nonmalignant conditions than for malignant conditions, a rare occurrence.⁷ This was probably due to the large number of patients treated that year for nasal polyps and lymphoid hypertrophy in the nasopharynx.

It does not seem logical to treat nonmalignant conditions with so powerful an agent as radium. However, the treatment is entirely safe in experienced hands, for only a fraction of the dose used for cancerous tissue is necessary. Some of these nonmalignant conditions are very distressing. I recall one man treated recently for Peyronie's disease. He was far more disturbed by the fibrous plaque than by a cancer of the rectum that had been treated and arrested several years previously.

CONCLUSIONS

Although confronted with an increasing incidence of malignant disease, cancer therapy has been given new hope by the phenomenal development of radium therapy. This development has been accelerated by simultaneous advances in the basic sciences and in biologic research. Much has been accomplished in arrest and palliation of carcinoma by radium roentgen rays and surgery, the only known methods of effective treatment. The words of caution uttered by Wickham in 1910 are still pertinent: "Radiumtherapy is indeed a very complex and delicate weapon to handle. Long and thorough personal experience is necessary in order to turn it to the best account, to learn to distinguish accurately the cases for which it is most suitable, and to avoid injuring patients either by badly proportioned doses or by depriving them of other therapeutic measures, which might prove more successful."¹⁶

Further progress can be achieved by earlier treatment in cases of accessible cancers. When the malignant lesion is not easily accessible (cancer of the esophagus, stomach, pancreas, gallbladder, small bowel and so forth) there is hope that further developments in the application of nuclear energy, such as the use of neutrons, may afford help in the future.

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CHANCROID OF THE UTERINE CERVIX

LOIS A DAY

CHANCROID or soft chancre, has long been known as a common venereal disease¹⁰ There are few publications dealing with the incidence of the infection in various populations and it is difficult to judge the frequency of the disease Fairly accurate data are available on its incidence in the armed forces but reports from State Health Departments indicate that probably it is frequently not reported as a communicable disease in the civilian population Most reports emphasize the fact that the disease is prone to occur in epidemics in communities following such events as fairs and carnivals Wartime conditions also favor an increased incidence with a subsequent fall when peacetime conditions return

The disease has not claimed the attention of the gynecologist as frequently as that of the urologist because of the relatively low incidence among women The sex incidence has been variously stated to be from ten to fifteen times greater among men than among women Strakosch and his co workers reported a series of 370 cases in which only seventy five patients were women It is believed that women more frequently harbor the causative organism in a saprophytic form on the mucous membranes without clinical evidence of the infection than men Bruck found the organisms on the vaginal mucous membrane of two women who did not show evidence of chancroidal infection but who were able to transmit their disease to men with whom they had sexual intercourse Saelhof reported that he found organisms similar to *Hemophilus ducreyi* in 12.8 per cent of thirty eight apparently uninfected women This ability to harbor the organisms on the mucous membrane without clinical evidence of the infection is not confined to women, as Brams reported finding the organism in the scrapings from the inner surface of the prepuce in five of thirty male Negroes whom he examined and Saelhof found the organism in 8.6 per cent of the apparently uninfected men whom he examined.

The disease is much more prevalent among Negroes and the economically unfortunate than among other groups In a report from the Cleveland City Hospital, Rauschkolb^{14 15} found the infection to be twice as common among Negroes as among whites The patients almost invariably gave a history of promiscuous intercourse showing, as others have observed, that the mode of infection is predominantly venereal. However it should be pointed out

that the secretions from the ulcerations are highly infectious and any break in the skin will serve as portal of entry. This fact explains the occurrence of the so-called professional chancroids on the fingers of physicians, nurses and hospital attendants.

The etiologic agent is *Hemophilus ducreyi*, the streptobacillus discovered by Ducrey in 1889 and confirmed by Unna in 1892. It is a gram-negative rod growing in short chains and cultured with difficulty on ordinary bacteriologic media. Sanderson and Greenblatt have successfully cultivated it in an atmosphere with reduced oxygen tension on a medium enriched with human blood. The disease has been produced in apes, monkeys and human subjects by the inoculation of a pure culture of the organism.

The chancroidal lesion in its earliest stage is a papule which soon undergoes ulceration. The ulcers vary from a few millimeters in diameter to the giant phagedenic chancroids, which originate in one of the small ulcers and extend peripherally. The ulcers are superficial with irregular edges and are filled with a grayish exudate. They bleed readily on manipulation and are very painful. Inguinal adenopathy occurs to some degree in almost all cases but the lesions are not invariably accompanied by the formation of a bubo. In the experience of the French authors the reported incidence of buboes is about 30 per cent among male patients. Rauschkolb^{14, 15} reported a 50 per cent incidence in a group of males. In contrast to syphilis the buboes in this disease are usually unilateral and painful. The simultaneous occurrence of two infecting organisms in the same lesion will often produce buboes that are not typical of either and lead to a confusing clinical picture.

The primary lesion is usually located on the genitalia or the surrounding area. Occasionally, extragenital lesions are encountered on the fingers, lips or tongue. In men the common sites of involvement are the frenum and the skin of the penis, in women the labia minora, clitoris, fourchet and vestibule.³ Because of the proximity of these parts in the female to the anus, it is frequently the site of a painful ulcer. Lesions of the uterine cervix have been infrequently reported in the American literature. French authors feel that they are not rare entities. Louste, Ducourtioux and Lotte reported in detail a case of chancroid of the cervix with associated inguinal adenopathy of the left groin. They stated in this paper that lesions of the cervix are fairly common and quoted Swart's study of a number of such cases published in his thesis in 1873. In view of the reports of various investigators that it is difficult to inoculate the mucous membrane and produce ulcers and the paucity of reports in the literature of chancroid of the cervix one wonders if these lesions are very common.

Some of the clinical characteristics of the lesion as seen on the cervix are well illustrated in the report of the two following cases

REPORT OF CASES

CASE 1—A woman, forty two years of age was seen at the Clinic in June 1944. She was sent by her physician for biopsy of a cervical lesion that he suspected might be malignant. She had consulted him because of burning and soreness of the vagina and pain that had been present in the lower part of the abdomen for a week. These symptoms had developed shortly after her return from Washington D. C., where she had been visiting her husband. She also had noted a slight amount of irritating whitish vaginal discharge.

When the patient was examined at the Clinic she was obviously distressed. Her temperature was normal. One tender lymph node was present in the left groin and three tender lymph nodes were present in the right groin. The pelvic examination was conducted with difficulty because of tenderness. Palpation of the uterus and adnexal regions did not reveal any abnormality. Examination with a speculum revealed a moderate amount of whitish vaginal discharge in which no *Trichomonas* or mycellal threads could be demonstrated. Mild vaginitis was present. The cervix was red and edematous and partially covered with a grayish white exudate that was removed without difficulty. Removal of the exudate revealed a superficial ulcer on the underlying mucous membrane which bled readily. There were three superficial ragged ulcers in the vaginal vault which varied from 0.5 to 2.5 cm. in diameter. They had a reddish serrated border and were partially covered with the same type of exudate as that on the cervix. Three darkfield examinations for *Treponema pallidum* were negative as were cultures for *Neisseria gonorrhoeae*. Examination of a smear from one of the ulcers revealed the presence of many gram negative bacilli resembling *Hemophilus ducreyi*. A flocculation test for syphilis was negative. After the completion of these examinations 4 gm. of sulfathiazole was administered orally each day. Three days later the patient was free of pain. The cervical lesion had begun to undergo involution and the vaginal ulcers were healing. At the end of a week's therapy the cervix was healed and the vaginal lesions had disappeared entirely. The inguinal lymph nodes were no longer palpable and the administration of sulfathiazole was discontinued. Two weeks later the results of a pelvic examination were negative as was a flocculation test. The patient was instructed to report to her local physician for monthly serologic tests for three months.

CASE 2—A woman aged twenty-one years came to the Clinic in September 1944 because of distress and discomfort in the lower part of the abdomen which were precipitated by sitting and which she said were due to some sores on her perineum. Her difficulty had started a week previously about five days after her husband had returned from the tropics. She had noticed a whitish watery irritating vaginal discharge that had caused vaginal burning and smarting. About the time of the onset of the pelvic pain she had had what she called "the flu". This illness had consisted of aching, chills and a temperature of 101° F. for the first two days. She had not felt well since and because of the distress in the lower part of the abdomen and discomfort occasioned by walking she had been in bed most of the time.

At the time of the initial examination the patient was obviously distressed and as she sat on the examining table she bent over and clutched her sides. Her temperature was 99.8° F. There were no palpable lymph nodes. Inspection of the external genitalia revealed several small superficial ulcers on the

red and inflamed mucous membrane of the introitus which was covered with a watery whitish discharge (fig 129, left) A similar ulcer was present on the left labium minus The vaginal speculum was introduced with difficulty because of the soreness of the parts The red, edematous, boggy cervix was covered with a whitish exudate (fig 129, right) There were no lesions on the mucous membrane of the vaginal fornices Microscopic examination of fresh smears did not disclose *Trichomonas* or mycelial threads and three darkfield examinations did not disclose *Treponema pallidum* There were many gram-negative bacilli which resembled *Hemophilus ducreyi* Cultures did not disclose *Neisseria gonorrhoeae* and flocculation tests for syphilis were negative

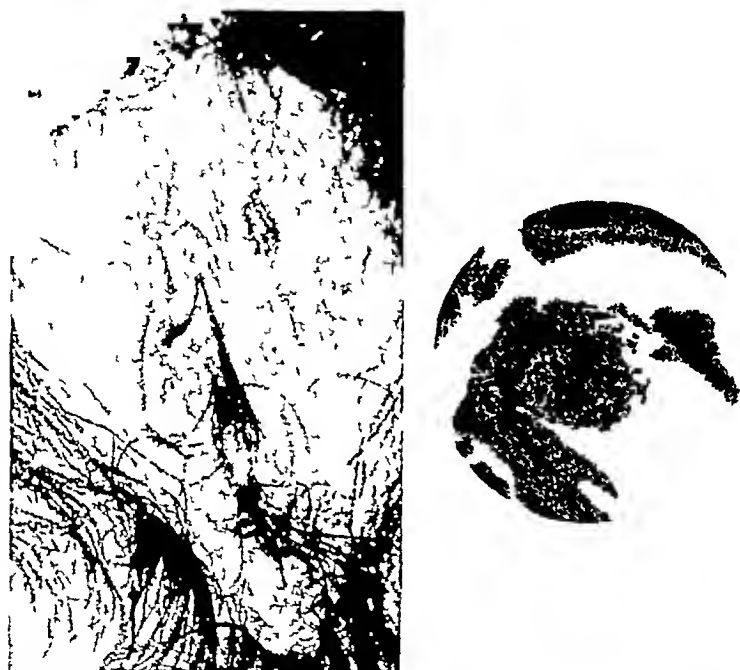


Fig 129—Left, Lesions on the vulva in case 2, right, chancroidal lesion of the cervix

The administration of sulfathiazole was started but had to be discontinued because of the nausea and vomiting it induced The patient was then given five intramuscular injections of 20,000 Oxford units each of the sodium salt of penicillin at intervals of three hours Two days later the pain had disappeared entirely A week later, the discharge had ceased, the ulcers had healed and the pelvic examination did not disclose any abnormality A month later, pelvic examination still failed to disclose any abnormality and the flocculation tests for syphilis were again negative She is to report at monthly intervals for two more months for serologic tests

Comment on Case 2—The patient's husband, a sailor, acquired a chancroid in January, 1944, while in the tropics and was treated with sulfanilamide The lesion rapidly underwent involution He returned home in September, 1944, and five days later his wife's ill-

ness began. The incubation period of chancroid is three to ten days. Examination of the husband did not reveal any lesion of the genitalia. Smears and cultures from the glans penis and prostatic cultures failed to demonstrate the presence of *Hemophilus ducreyi*. It would appear that he was a carrier of the organism in spite of the failure of our efforts to demonstrate it.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cervical lesions is an ever present challenge to the gynecologist. The first consideration is that of deciding whether the lesion is of inflammatory or neoplastic origin. It is difficult at times to make this differentiation. Pund and Greenblatt^{5, 13} have called attention to this problem in several publications. They reported two cases of granuloma venereum of the cervix in which the lesion more nearly resembled carcinoma than granuloma. They expressed the belief that biopsy of the lesion is of great importance, particularly in the late stages, in ruling out the possibility of malignant changes and also in establishing the diagnosis in this disease. Heyman and his co-workers expressed the opinion that the pathologic changes in the chancroidal ulcer are specific enough to enable one to establish a diagnosis. They pointed out that this method is not well suited to use when the lesion is in an early stage because of the discomfort that it causes the patient and that for such lesions other methods of diagnosis are of greater value. In our two cases the clinical history and symptoms made the differential diagnosis between an inflammatory lesion and a neoplasm fairly obvious. The multiplicity of the ulcers, their short period of duration and the associated pain suggested that they were not of neoplastic origin.

A number of other laboratory procedures have been worked out to supplement the clinical findings and minimize errors in diagnosis. Smears and cultures made from the lesions for *Hemophilus ducreyi* and *Neisseria gonorrhoeae* are of help in further establishing the diagnosis. Gram's stain will demonstrate the characteristic short, plump rods with rounded ends of *Hemophilus ducreyi*. In early lesions that are not secondarily infected it is much easier to identify the organisms even though they may be few than in other lesions. It is often advantageous to use the Pappenheim stain since it reveals the characteristic "safety pin" forms. Under suitable conditions of reduced oxygen tension the organisms can be cultivated on a medium enriched with rabbits or human blood without too much difficulty.

The frequency of the occurrence of *Hemophilus ducreyi* and *Treponema pallidum* in the same genital lesion makes it imperative

that every such lesion be regarded as a chancre until proved otherwise. Repeated darkfield examinations for *Treponema pallidum* should be done on every ulcerative lesion of the genitalia. At least three such examinations should be done on three different days and no medication should be given during this time. Flocculation tests should be checked for a period of three months after the ulcer has healed. Knott and his co-workers warned that biologic false positive reactions for syphilis occur with surprising frequency in cases of chancroid, lymphogranuloma venereum and other types of non-syphilitic genital lesions. They emphasize that antisyphilitic treatment should not be instituted when a patient has a darkfield negative genital lesion and a positive serologic reaction of low titer for syphilis, unless positive reactions are confirmed by repeated examinations. They recommended that the reagin titer should be followed by repeated quantitative tests.

Though opinions vary as to the specificity and sensitivity of the cutaneous test with the Ducrey vaccine, this test has been widely used as a method of diagnosis.⁷ The limitations of the value of this test lie in several facts. Since a positive reaction persists for years after the initial infection, one cannot be sure whether a positive reaction represents the existing infection or a previous one. The reaction usually does not become positive for a period of five weeks after the initial infection though occasionally positive reactions are seen in five to ten days.

Auto-inoculation, a method of diagnosis, has the disadvantages of the development of a new area of infection that is not devoid of danger and of delaying the treatment for a period of at least forty eight hours.

A review of the various diagnostic procedures that may be employed reveals that no one test alone is infallible but that the diagnosis must be arrived at by employing several methods. These, combined with the history and clinical picture, will lead to an accurate diagnosis.

TREATMENT

Until recently there was no effective therapeutic agent for the treatment of chancroid. In the past, treatment was usually carried out over several weeks at the best and in many cases it was necessary to continue it for many weeks. In 1938 Hanschell reported the successful use of sulfanilamide. The lesions healed rapidly in five to ten days without formation of a scar. Sulfanilamide has the further advantage of not affecting the clinical course or the serologic reaction for syphilis. Since this report others have reported^{4, 8} a similar group of cases in which various sulfa drugs including sulfathiazole have been used with dramatic success.

Penicillin was effective in the treatment of my patient who did not tolerate the sulfa drug Strakosch and his associates reported that they observed the healing of chancroidal lesions in a group of twenty five patients who were being treated for primary and secondary syphilis with penicillin. They noted that if the lesions were small they healed in seven and a half days. In five cases the patients needed additional treatment with sulfathiazole. The dosage of penicillin varied from 300,000 units for ten patients to 600,000 for fifteen patients over a seven and a half day period. Greenblatt⁵ in discussing the paper of Strakosch and associates stated that in his experience the treatment of three patients with 100,000, 200,000 and 600,000 units of penicillin respectively had been ineffective. Penicillin also has the objectionable property of masking undiagnosed syphilitic lesions and probably should not be used except for the occasional patient who does not tolerate sulfathiazole.

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HABITUAL ABORTION

ARTHUR B HUNT

SUCH great confusion is attendant on the problem of habitual abortion that there is almost no uniformity of opinion among obstetricians and gynecologists concerning this important phase of infertility. The disagreement centers around an acceptable definition of the term and especially around the value of treatment for the condition. Many of the discussions of a definition of the term "habitual abortion" seem only of academic importance and yet it is obviously of practical importance that all have in mind a clear-cut entity when the subject is studied and when results of such study are reported. In the most rigid definition of the term it is applied only to the case in which the entire child bearing career is composed of three or more spontaneous abortions in the first trimester or the first half of gestation. Some obstetricians loosely regard the condition as a tendency to abort or undergo fruitless pregnancies regardless of how the sequence of these failures falls in with the delivery of living infants. Others confine the use of the term to cases in which at least two or more spontaneous abortions have occurred since the birth of any living infants.

The expressed attitude of physicians on habitual abortion varies from one of almost complete cynicism and therapeutic nihilism on the one hand to that of confident enthusiasm on the other. Malpas perhaps best expressed the conservative attitude by stating that chance best explains recurrent abortion in a given individual and that except in the presence of such tangible factors as the so-called toxemias of pregnancy and complicated heart disease patients with sequential fruitless pregnancies do as well in future pregnancies without treatment as with it. Javert and Stander, on the other hand reported that in 100 per cent of forty six cases of threatened, spontaneous and habitual abortion, abortions occurred when no treatment was given whereas they occurred in only 9 per cent of thirty three such cases in which treatment was given. Their data on habitual abortion (three or more consecutive abortions) indicate that abortion occurred in all of eight cases in which no treatment was given and in one of fourteen cases (7 per cent) in which treatment was employed.

ETIOLOGIC FACTORS IN HABITUAL ABORTION

Pathologic physiology along the following lines has been incriminated in habitual abortion: defective oogenesis or spermatogenesis

hypofunction of the thyroid gland, serologic disturbances, vitamin deficiencies, especially of vitamins E, C and K, disturbances of glycogen metabolism and storage of glycogen in the endometrium, certain endocrine disturbances of the anterior pituitary gland and the corpus luteum, and disturbances in the production of estrogen.

Hertig and Livingstone and many others (since Mall) have shown that in approximately two thirds of spontaneous abortions the ovum is grossly defective. The extent to which this observation applies in cases of habitual abortion depends somewhat on the analysis of the statistician.

Absence of oogenesis is diagnosed in a rough way by endometrial biopsy either premenstrually or by serial endometrial biopsies in long periods of amenorrhea. When oogenesis does not occur, the biopsies fail to reveal any secretory effect. The role of defective spermatogenesis in habitual abortion is poorly understood at present. There is more agreement concerning low basal metabolic rates among women who have habitual abortion, and administration of desiccated thyroid in proper doses as measured by the rise in the basal metabolic rate to within the limits of normal is indicated. The role of serologic factors, such as the Rh and the A and B factors, in repeated abortion has been discussed by Levine. He and others^{4, 14} have data to show that the Rh factor is unimportant in the general incidence of habitual abortion. Studies on vitamins C and K are interesting and suggestive but their importance in causing repeated abortion has not been established definitely. A few years ago the use of vitamin E gained some favor in the treatment of habitual abortion based on its success in several small series of cases wherein no other therapeutic agent was employed. The majority of obstetricians and gynecologists probably now doubt its value but many of them, while skeptical of any worth in its use, still employ it since it probably does no harm and may be of some unknown value to the human being as it is to the rat. Cows apparently do not need it to conceive and reproduce successfully.¹⁰ Its value in habitual abortion in the human being is difficult to demonstrate objectively. Hughes' studies suggested endometrial deficiencies in glycogen and certain enzymes in cases of abortion and ovarian dysfunction. These may represent poor ovarian function or a refractory state in the endometrium.

Detailed studies of pituitary and ovarian function in the pregnancies of patients subject to habitual abortion have been rather sketchy. Hamblen has been disappointed with the inability of adequate progesterone therapy to raise the level of pregnandiol in the urine. He has observed in rare cases, as I have, that very low levels of pregnandiol (even to complete absence on one assay in preg-

nancy) will adjust themselves and the pregnancy will continue Vaux and Rakoff have presented some evidence of low levels of estrin and pregnandiol for which they think treatment with estrogen combined with progesterone is merited Their results from this treatment seem encouraging

INVESTIGATION OF THE COUPLE IN CASES OF HABITUAL ABORTION

Miminal examination of the male is often satisfactorily effected by thorough examination of satisfactory specimens of sperm If this gives evidence of faulty spermatogenesis, general and urologic examinations together with a determination of the basal metabolic rate are indicated and the usual therapeutic measures should follow although the results admittedly are not as yet, well established

In addition to a careful history and examination the woman should have a test of the basal metabolic rate and a premenstrual endometrial biopsy If assays for gonadotropic hormone, estrogen and pregnandiol are available, they are perhaps worth while if done at the proper time of the menstrual cycle Javert and Stander were of the opinion that determinations of vitamin C and prothrombin time are valuable

Hertig and Livingstone wisely advised that pathologic states pertinent to the etiology of habitual abortion be corrected before conception with the hope that a higher incidence of normal ova be obtained This is obviously good advice but in practice it is often difficult to demonstrate tangible faults and correct them Also much of the prophylactic treatment against abortion cannot be given until conception has occurred The diet and intake of vitamins can be improved before conception A low basal metabolic rate should be corrected then and occasionally demonstrable deficiencies in ovarian or pituitary function can be improved More often no such pathologic state can be uncovered before conception and the patient's fertility as far as conceiving goes is good

PROPHYLACTIC TREATMENT OF HABITUAL ABORTION

Results are much better if patients with habitual abortion are treated prophylactically as soon as the fact of conception can be demonstrated rather than to employ active treatment after abortion as evidenced by bleeding or cramping or both, is actually in progress

Therapeutic agents that have been used with varying frequency in the treatment of habitual abortion are progesterone vitamin E desiccated thyroid estrogen, vitamins C and K and gonadotropins

Many reports are concerned with the use of only one of these agents while others deal with two or more

For several years my colleagues and I have in general been more interested in giving these patients a combined method of treatment. In this method we use all medicaments which theoretically play a part in maintaining pregnancy and we are of the opinion that the patient is more likely to be placed in a normal physiologic environment for successful reproduction than with only one type of treatment. This method may be criticized as not being scientific for we do not ascertain which specific deficiency exists in a given case of habitual abortion. However, we frankly are more interested in salvaging a baby if possible for the individual patient. Furthermore, the composite method of treatment in itself can be evaluated and this is perhaps as far as we should go in fairness to the patient as long as present knowledge of habitual abortion lies somewhere between outright empiricism and certain knowledge

Progesterone.—The exact dose of progesterone required to correct a deficiency of this substance in a given case of habitual abortion is probably unknown. Most observers believe it is much greater than was originally supposed. Because of its expense the patient's means may be the deciding factor as to how much she can take as a daily dose for the several months that it may be required. Anhydrohydroxy progesterone, the preparation for oral administration, seems less efficacious milligram for milligram in substituting for a deficient corpus luteum than in progesterone itself, since about five times as large a dose is required for an equal effect. However, the decreased cost and the convenience of steady administration of the drug are the advantages of the oral preparation. From 10 to 30 mg of anhydrohydroxy progesterone is given daily and in many cases progesterone also is administered intramuscularly in doses from 2 to 10 mg every other day or twice a week. This treatment is carried on until the first four and a half to five months of gestation have passed. If spotting or cramping ensues, the dose of progesterone given intramuscularly should be increased to from 10 to 20 mg and it should be given daily until signs of abortion subside or the abortion becomes inevitable or complete.

Estrogen—For at least five years my colleagues and I, largely through the influence of one associate, Dr Lois A. Day, have used estrogen in the combined or composite method of treatment. It has generally been conceded that progesterone and estrogen are antagonistic hormones and, therefore, the latter because of its motile effect on the uterus is contraindicated in the treatment of abortion. There are, however, equally good reasons for its use. For example, the corpus luteum produces both estrogen and proges-

terone Both hormones seem needed for the proper metabolism of each one As much and perhaps more estrogen is produced in the luteal phase than in the estrogenic phase of the menstrual cycle Vaux and Rakoff discussed these and other considerations when they expressed their opinion that estrogens are of value in the prophylaxis of abortion Diethylstilbestrol is the drug of choice with us because it is less expensive than other preparations and is effective when administered orally The dose employed has varied from 1 to 10 mg daily, usually the lower range of this dose is employed especially in the early weeks of pregnancy

Vitamin E—Opinion varies sharply as to whether or not this substance has any value in the prevention of abortion If it is used in composite treatment, a dose of about 50 mg. a day of alpha tocopherol is given.

Thyroid—It has long been known that pregnant patients who have significantly lowered basal metabolic rates tend to abort and also tend to carry to term when the deficiency is properly corrected by the administration of desiccated thyroid The basal metabolic rate should be raised from its low level to about -5 to 0 per cent or possibly slightly higher during pregnancy if no symptoms of excessive dosage appear Several of my colleagues and I also are of the opinion that it is worth while to administer thyroid substance carefully to women who are afflicted with habitual abortion even though the basal metabolic rate is not markedly lowered It must be remembered that the potency of the various thyroid substances varies considerably according to the manufacturer

Gonadotropins—Hamblen and others still have a place for gonadotropins in their treatment of habitual abortion The various commercial preparations may be used but at the Clinic we prefer pregnancy serum, a crude product which probably contains several hormones The excellent results reported by Rosenfeld in 1938 have been largely overlooked in the literature. In his cases pregnancy serum was the only medicament employed except for the inconsistent use of vitamin D Rosenfeld reported only one failure in twenty cases In the one instance of failure the patient was carried to the twenty fourth week when premature separation of the placenta interrupted the pregnancy Her five previous pregnancies had not gone past the eighth week Rosenfeld's twenty patients previously had had a total of eighty six pregnancies and only thirteen babies had been delivered He attributed the first use of pregnancy serum in habitual abortion to Sellheim who with this mode of therapy had carried eight of nine patients to term However several of Sellheim's patients could hardly be said to have true habitual abortion Because of Rosenfeld's study and for theoretical reasons

I still use pregnancy serum in the composite treatment of habitual abortion. Twenty c.c. of the sterile serum from a pregnant donor who has a negative flocculation test for syphilis, is injected intramuscularly each month up to the sixth month. It is probably wise to avoid the use of whole blood for Rh-negative women because of the danger of iso-immunizing them to the Rh factor. The use of any human serum, such as this, incurs the remote but real risk of transmitting infectious jaundice to the recipient which may not develop until some weeks later. There is as yet no practical test for determining whether a given batch of serum is entirely safe in this regard.

Diet.—Too little emphasis has been placed on the importance of diet in habitual abortion. The well-known fact that a high protein diet increases production of eggs in hens and production of milk in cows may have significance for human beings. When the farmer is no longer interested in egg or milk production in a given set of animals, he stops the heavy feeding of protein and substitutes carbohydrate (corn), production falls and the animals gain weight for the market. Therefore, a high protein diet and reasonable administration of multiple vitamins seem indicated even before conception and throughout the period of pregnancy and lactation. Dietary correction of patients that are either overweight or underweight is advisable before conception also.

General Measures—Several general measures, such as rest in bed, have always been used in the hope of preventing abortion. The avoidance of coitus is always desirable not only because of mechanical reasons but possibly because of untoward endocrine effects. Moderation in daily living is a common sense course to be advised.

THE QUESTION OF FETAL ANOMALIES IN CASES OF HABITUAL ABORTION

Since it is well known that the majority of embryos in spontaneous abortion have major defects, it has often been feared that the treatment of habitual abortion will prolong the life of such embryos to result at birth in a large number of grossly deformed babies. Hertig and Livingstone as well as Shute in their reviews of the question have shown that to some extent this is probably true. The incidence of anomalies in such cases does rise but no higher than in the neighborhood of 2 to 4 per cent of all such babies delivered after treatment for habitual abortion. This has not in general been regarded as reason in itself for giving up the attempt to treat cases of recurrent abortion.

RESULT OF TREATMENT

True habitual abortion, that is three or more spontaneous abortions in the same case, without any other pregnancies, is a rare condition. Javert and Stander found it occurred in one among 411 pregnant women in a series of 24,289 admissions of pregnant women to the New York Hospital. Because of its rarity it is difficult if not impossible for one physician to report well-controlled results in an impressive series of cases. Therefore collective reviews of reported cases have to be depended on for this information and these cases meet or fail to meet the varying definitions of the syndrome.

Hertig and Livingstone collected 681 cases of so-called habitual abortion and observed that 564 patients (82.8 per cent) went through pregnancy on treatment. Kotz, Parker and Kaufman reviewed the reports of 273 cases. Two hundred and sixteen patients (79.1 per cent) went through pregnancy while receiving treatment. There was of course considerable duplication in these two series. Kotz and his associates also reported seventeen cases of true habitual abortion with one failure of treatment. Thus 94.1 per cent of this small series of patients went through pregnancy successfully.

COMMENT

Those who feel that the treatment of habitual abortion has no value point out that most reports of treatment in cases of recurrent abortion are favorable regardless of the drug or drugs used and regardless of the dosage. This, however, may not be as illogical as it seems at first. The various hormones and vitamins used in treatment of habitual abortion are often not too unrelated chemically or in their physiologic action. Some workers are of the opinion that the thyroid acts through the pituitary to increase luteinization and that vitamin C stimulates the growth of the corpus luteum (which in itself has large amounts of this vitamin).^{8, 10} Gonadotropins in addition to their substitution effect for the pituitary may stimulate the production of estrogen and progesterone from the ovary. The more direct effect of estrogen and progesterone has been mentioned.

With the possible exception of desiccated thyroid the dosage of which is determined by the basal metabolic rate, the exact dose of the various drugs used for habitual abortion is still largely empiric. There are several reports of good results in the treatment of habitual abortion with seemingly minute doses of drugs. I will take progesterone medication as an example. As nearly as can now be ascertained, the requirements of progesterone from the corpus luteum and the placenta vary from 5 to 50 mg daily and rise from the lower figure upward as the placenta takes over the function of making progesterone. It is not necessary or perhaps desirable that

all of the required progesterone be supplied by substitution therapy. There is little proof that the corpus luteum any more than any other endocrine gland functions on an all or none basis. It is more probably making progesterone but not enough. Usually when substitution therapy is complete and the doses reach 100 per cent of requirements, the function of gland involved is depressed. Moderate doses probably supplement a defective corpus luteum better than either homeopathic or excessive ones.

Treatment for habitual abortion has an indirect effect on the patient which Hamblen has called "psychologic conditioning." The patient is encouraged by the earnest, orderly method of treatment prescribed and by the implication that the prognosis may not be hopeless. She is encouraged to live more carefully and to co-operate in treatment.

It can be observed that in many series of reported cases the prognosis is no worse and may even be slightly better in treated cases of recurrent abortion as the number of abortions in the past history increases. The report of Kotz and his associates is an example of this. Those who decry the value of treatment must take note of this. Even Malpas has reported that after the third spontaneous abortion, the prognosis for a successful pregnancy is progressively poorer if treatment is not given. Of course there will always be two groups of patients that plague and embarrass physicians who enthusiastically view the treatment of habitual abortion. One type of patient, wearied and discouraged by past treatment for habitual abortion, appears for prenatal care too late for treatment but nevertheless completes her pregnancy successfully. The other type of patient continues to abort or miscarry time after time in spite of any and all therapy. The latter type of patient has good enough genital physiology to conceive but not good enough reproductive function to carry her through pregnancy no matter what type of semi-empiric treatment available today is employed.

However, until well-controlled series of cases of habitual abortion without treatment are presented that match in results those that have been reported with treatment the obstetrician and gynecologist are still justified in attempting to treat women for habitual abortion. No instances of maternal damage have yet come to light from reasonable attempts at such treatment. The purpose and detailed method of composite treatment to place a woman in as favorable physiologic environment as possible for successful reproduction have been outlined.

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THE MEDICAL CLINICS

of

NORTH AMERICA

BOSTON NUMBER

SYMPOSIUM ON SPECIFIC METHODS OF TREATMENT

CLINICAL EXPERIENCE WITH STREPTOMYCIN

A Study of 50 Cases

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AND WILLIAM L. HEWITT, M.D. ‡

In this presentation we propose to sum up our experience with streptomycin in the treatment of fifty infections of various types at the Massachusetts Memorial Hospitals. The distribution of the cases is shown in Table 1.

TABLE 1 — DISTRIBUTION OF CASES IN THE SERIES

Diseases	Total No. of Cases
Urinary tract infections	28
H. influenzae meningitis	10
B. pyocyaneus sepsis	4
Typhoid fever	2
Brucellosis	1
Salmonella infections	4
Urinary tract	2
Intestinal tract	2
Miliary tuberculosis with meningitis	1
Total	<u>50</u>

From the Evans and Haynes Memorials, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

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URINARY TRACT INFECTIONS

There were twenty-eight instances of urinary tract infection. In fifteen cases there was a single infecting organism and in thirteen the infection was a mixed one. Clinical improvement frequently occurred with a persistent bacilluria. In the group as a whole, the average daily dose of streptomycin was 1.08 gm, which was given for an average of 9.4 days. An average of the total dose per patient was 10.27 gm. The results of treatment in the two groups of infection are shown in Table 2. It will be noted that better results were obtained in patients who had a single infecting organism and that clinical improvement as reflected in the course of the fever and regression of local signs of infection often occurred without complete sterilization of the urine. The most susceptible organisms were *Bacillus proteus* and *Hemophilus* in-

TABLE 2 —URINARY TRACT INFECTIONS

Type of Infection	Number of Cases	Satisfactory Clinical Response	Unsatisfactory Clinical Response	Bacteriuria after Treatment	
				Present	Absent
Single organism	15	10	5	6	9
<i>E. coli</i>	12	7	5	8	4
<i>B. proteus</i>	2	2	—	0	2
<i>H. influenzae</i>	1	1	—	0	1
Mixed Infections	13	6	7	10	3
<i>E. coli</i>	9	3	6	8	1
<i>Ps. aeruginosa</i>	5	2	3	5	0
<i>B. proteus</i>	5	2	3	3	2
<i>A. aerogenes</i>	2	1	1	0	2
All cases	28	16	12	16	12

influenzae, and, to a lesser extent, the colon bacillus. Only four of the twelve patients with colon bacillus infection had a sterile urine at the end of their treatment.

Figure 130 illustrates the course of events in a patient with a single type of infection. In this case there was a prompt disappearance of the symptoms and signs of infection and a sterilization of the urine.

The mixed infections of the urine were more resistant to treatment than the single infections. This was due to the fact that the anatomical lesions of the urinary tract were more complex and many of the organisms were extremely resistant to the action of streptomycin. In some instances it was possible to eliminate the susceptible organisms from the urine, and the more resistant ones would persist. This is illustrated in Figure 131. Another feature that is noticeable is the appearance in the urine of microorganisms that were not present when streptomycin

was first started. These organisms may have been present in small numbers before treatment was started, but were overgrown by the others. When the susceptible organisms were suppressed, the less sensitive ones appeared.

With streptomycin it was possible to control infections in preparation of patients for surgical treatment. In cases such as that shown in

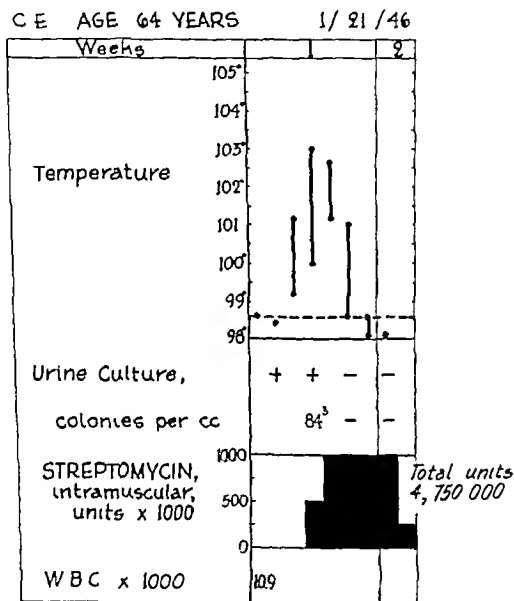


Fig 130—Chart showing course of events in a patient with a urinary tract infection due to *Bacillus proteus*.

Figure 132, the constitutional symptoms of infection were controlled in spite of failure to sterilize the urine. In this way streptomycin was effective as a preoperative treatment.

General Comment—Streptomycin has been effective in certain urinary tract infections. The results have been limited by a number of variables including such factors as the species of organism causing the infection, the sensitivity of the organisms to streptomycin, the reaction of the urine, the presence of the anatomical lesions that inter-

fere with the free flow of urine, or a wound infection such as occurs following transurethral resection of the prostate. It is well, then, before starting treatment, to be fully acquainted with all these variables and to plan the treatment accordingly. These limiting factors will now be discussed.

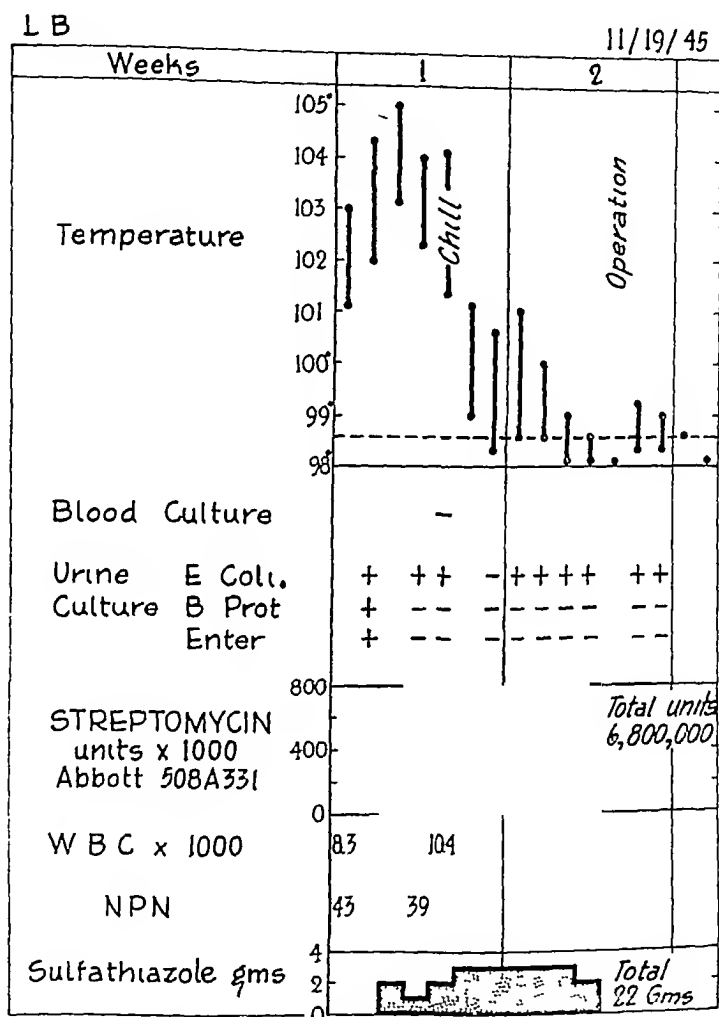


Fig. 131—Chart illustrating that some species of microorganisms are eliminated from the urine following streptomycin, others persist in spite of the disappearance of the constitutional symptoms of infection.

Infecting Organisms—The microorganisms infecting the genitourinary tract are very numerous indeed, and since there is a wide variation in the sensitivity of various microbes to streptomycin, it is absolutely necessary to know what species of organism are causing the infection before treatment is started if one expects to obtain the best results,

and interpret the failures as well as the successes. In our own experience, the infecting organisms have included *Escherichia coli*, *Bacillus proteus*, *Bacillus pyocyaneus*, *Aerobacter aerogenes*, *Hemophilus influenzae*, and *Salmonella*. Other organisms which may be encountered are staphylococci, *Streptococcus faecalis*, enterococci and typhoid bacilli.

Sensitivity of Organisms—One of the most striking features of these infections is the rapidity with which streptomycin fastness develops

PYELONEPHRITIS

F W D JR. AGE 24 YEARS

11/3/45

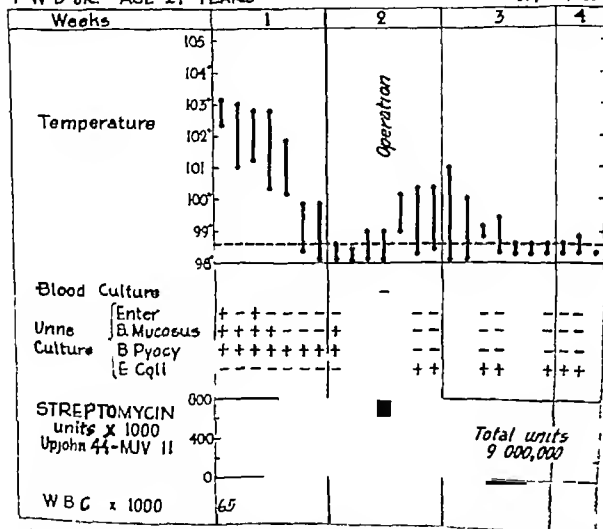


Fig 132.—Chart showing course of events in a mixed infection. Certain organisms disappeared following streptomycin and *Escherichia coli* appeared in the urine while the patient was under treatment

This feature may be one of the major factors in explaining the failure of streptomycin therapy in gram negative infections of the urinary tract. In all the cases which we studied and in which the urine was not sterilized by streptomycin there was an increase in the resistance of the organisms to the drug. Table 3 shows this increase in resistance very well. The persistence of infections and the appearance of resistant strains after streptomycin treatment has already been noted in

others The evidence seems good that the resistance to streptomycin is acquired in vivo during treatment and this is the important fact from the viewpoint of practical therapy

It is a matter of the highest importance that the mechanism of this acquired resistance be understood, for the reason that it may be pos

TABLE 3 —SENSITIVITY OF ORGANISMS

Case	Organism	Resistance of Organism in Micrograms per cc	
		Before Treatment	After Treatment
1	E coli	8	200
	B pyocyaneus	12	Absent
	B mucosus capsulatus	8	Absent
2	E coli	4	200
3	E coli	8	200
4	B proteus	4	Absent
5	B pyocyaneus	12	Absent
	St faecalis	8	Absent
	B mucosus	8	Absent
	E coli	—	50
6	B proteus	4	Absent
7	E coli	12	500
8	E coli	—	50
9	E coli	12	Absent
10	E coli	16	500
11	E coli	10	200
	Salmonella	8	50
12	B pyocyaneus	10	Absent
13	B pyocyaneus	12	50
	E coli	4	200
14	E coli	10	200
15	E coli	4	Absent
16	E coli	10	200
17	E coli	8	200
	B proteus	8	Absent
	B pyocyaneus	12	Absent
	B mucosus	12	Absent
18	E coli	2	500
	B mucosus	2	500
19	E coli	20	200

sible in some instances to prevent it There are two views at present The first suggests that resistant organisms which are obtained after treatment are derived from originally sensitive ones through some change in their growth requirements which are conditioned by the exposure to streptomycin The second view is that the resistant organisms are present in the original population of bacteria and continue to

survive and flourish after the sensitive organisms have been eliminated. From the practical viewpoint, however it can be shown repeatedly that organisms isolated from the urine before treatment are sensitive *in vitro*, whereas those obtained after treatment are extremely resistant. Moreover patients fail to respond to treatment with doses of streptomycin which should be adequate to sterilize the urine, if one can judge from the original sensitivity of the strains and the concentration of the streptomycin in the blood and urine. The development of acquired resistance *in vivo* may explain many of the failures of treatment.

The Reaction of the Urine—It has been demonstrated that streptomycin is much less effective in an acid medium than in an alkaline one. It would be well therefore, to make the urine alkaline in all patients in order to obtain the optimum effect. It is not implied, however, that streptomycin will be ineffective in an acid urine for the reason that some patients have recovered following the use of streptomycin when the urine was acid.

The Importance of Obstruction—When there is an obstructive lesion in the urinary tract, or a foreign body such as a stone, it has been impossible for us to sterilize the urine. A reduction of the number of bacteria in the urine is possible but when stasis persists, organisms increase soon after streptomycin is discontinued.

Recommendations for Treatment of Urinary Tract Infections—

1. Complete study of genitourinary tract to include renal function and the determination of pathologic lesions

2. Isolation and identification of all infecting bacteria which are present, with their sensitivity to streptomycin

3. Determination of the reaction of the urine.

4. The use of maximum doses of streptomycin early in the course of treatment.

5. Treatment with streptomycin should be discontinued if organisms develop resistance to the drug.

6. The use of other agents such as penicillin the sulfonamides or mandelic acid along with streptomycin should be explored

HEMOPHILUS INFLUENZAE MENINGITIS

Ten patients with influenzal meningitis were treated with streptomycin and eight recovered completely. Five of the patients were under 3 years of age, and the remaining five varied in age between 3 and 5 years. The two fatal cases were 4 and 8 months of age respectively. In eight of the ten cases the infecting organism was a Type B Hemophilus influenzae the other two strains were untypable. Six of the ten patients had bacteremia, and six of the patients had influenza bacilli in either the nose or the throat at the beginning of treatment. One patient developed an intercurrent Staphylococcus aureus bacteremia and meningitis and recovered following the use of penicillin. Of the two fatal

cases, one child died of an extensive staphylococcus pneumonia, and the other had an infection due to an untypable organism which failed to respond to treatment

Methods of Treatment.—All the patients received streptomycin intramuscularly and intrathecally. The intramuscular injections were given every three hours for a period varying from five to ten days, and the total amount varied from 2.75 to 9.5 gm, the average being 6.5 gm. In general, 0.05 to 0.125 gm were given intramuscularly every three

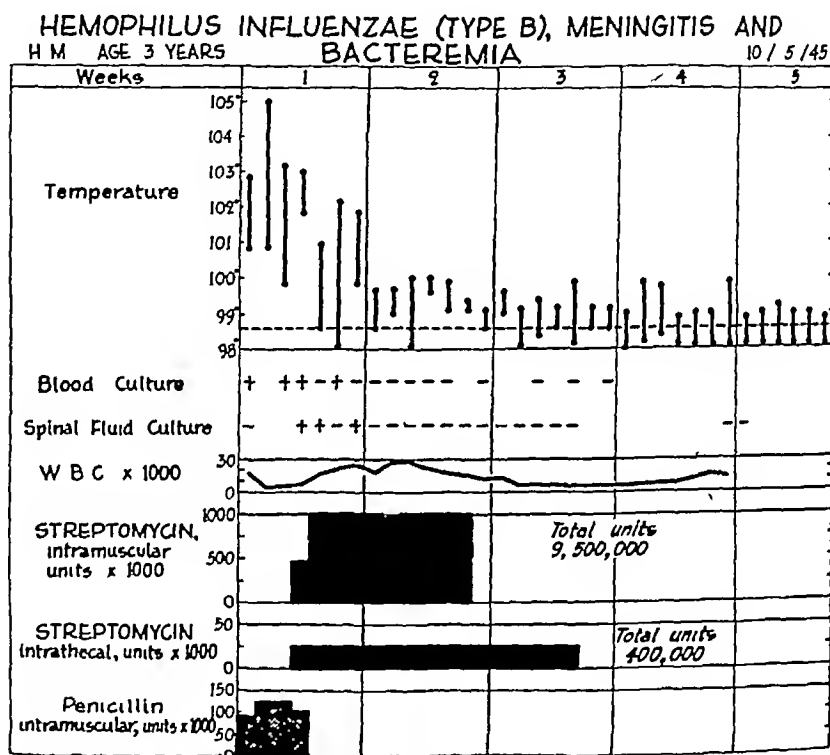


Fig 133—Chart illustrating the course of events in a patient with *Hemophilus influenzae* meningitis and bacteremia. The blood and cerebrospinal fluid were sterilized promptly and the patient made a complete recovery.

hours. The average amount given intrathecally was 0.35 gm. Daily injections of 25 to 50 mg were given for a period of eight to fourteen days.

With this treatment schedule the bacteremia disappeared within twenty-four hours, and the spinal fluid was sterilized in eight of the ten cases within twenty-four to seventy-two hours.

Several experiences during the treatment of patients with influenzal meningitis have stressed the importance of making careful bacteriological studies of all patients during the course of the disease. In two of

desirable to establish the diagnosis early, and to inject streptomycin both intramuscularly for at least three to four days and intrathecally for a period of at least seven days. The duration of treatment will depend upon the clinical course and response of the patient to treatment. Repeated bacteriologic examinations of the secretions of the nose and throat are desirable in order to detect a change in the bacterial flora which may be significant.

SALMONELLA INFECTIONS

There were four cases of *Salmonella* infections in the group, all paratyphoid Group B. One case was an instance of cystopyelitis, one was a mixed infection of the urinary tract with *Escherichia coli*, two were examples of gastrointestinal infections—one was acute and the other was complicated by osteomyelitis of the vertebrae with a psoas abscess. There were two deaths, one in a 73 year old man with acute gastroenteritis of five days' duration who was admitted in a state of shock and dehydration, with signs of renal insufficiency and acidosis. The illness was further complicated by the development of a Type IX pneumococcic bacteremia. Streptomycin was given for only two days, and although the urine was sterilized, the patient expired.

The problem of mixed infections again asserted itself in the course of these cases. In one, the *Salmonella* organisms appeared in the urine of a patient who was being treated for an *E. coli* infection of the urinary tract with bacteremia. In another, the infection was associated with a Type IX pneumococcic infection. These observations stress the importance of careful bacteriologic studies so that the treatment may be appropriate, and the results may be properly evaluated.

On the whole, the treatment of these cases with streptomycin was disappointing, since it was not possible to sterilize the urine permanently in any case.

BACILLUS PYOCYANEUS INFECTION WITH BACTEREMIA

Different strains of *Pseudomonas aeruginosa* vary enormously in their sensitivity to streptomycin. Therefore it is not very surprising that the results so far have been irregular. There is some evidence that susceptible cells may be destroyed and insensitive cells will continue to grow even in high concentrations of streptomycin. We have observed four patients with *Bacillus pyocyaneus* infection and bacteremia. One arose in the urinary tract and was complicated by an osteomyelitis of the spine. One occurred during the course of an acute lupus erythematosus, a third complicated chronic lymphoid leukemia, and a fourth developed in a patient with cholelithiasis and cholecystitis. Three of the four patients died, and the fourth, who recovered, was the man with the urinary tract infection, bacteremia, and osteomyelitis of the

spine The detailed clinical study of these patients, with a review of the literature, will be reported later

In two of the three fatal cases it was possible to sterilize the blood of organisms, but in the third the organisms persisted and the resistance was found to be 8 units per cc. for the first organisms isolated from the blood and 500 units per cc. several days later In one of the fatal cases *E. coli* appeared in the circulating blood after *B. pyocyaneus* had been removed. This experience stresses once again the importance of doing repeated bacteriologic studies of the blood and other sites of infection, and the invasion of the tissues by organisms which are not susceptible to the action of streptomycin in the concentration to which they are exposed.

It is recommended that all patients with *B. pyocyaneus* infection with bacteremia should be treated promptly with streptomycin starting with 4 gm. a day and continuing for at least seven to ten days to determine whether the infection can be controlled The organisms should be tested promptly for their sensitivity to streptomycin, and if they are susceptible within therapeutic range, the treatment should be continued This may be a field for combined treatment with other agents such as the sulfonamides

MISCELLANEOUS INFECTIONS

Brucellosis—We have had an opportunity of treating only a single patient with brucellosis due to *Brucella suis* (Fig. 135) However certain observations worthy of comment were made. There was a temporary clearing of the bacteremia while the patient was receiving streptomycin with a recurrence soon after stopping it. There was no abrupt change in the course of the temperature curve The results which have been recorded so far have been disappointing, for the reason that the course of the disease does not appear to be shortened and recurrences of bacteremia and fever are frequent following the discontinuance of the drug Long term therapy will be needed to determine whether the course of the disease can be altered.

Typhoid Fever—There were two patients with typhoid fever One was reported recently by Anderson and Jewell The other is a more recent case in which 5 gm. of streptomycin a day were given for a period of ten days without altering the course of the disease An insufficient number of patients have been treated to determine the effect of streptomycin on the fatality rate in typhoid fever From the reports of cases which have been published, there is as yet no conclusive evidence that the course of the disease is shortened More cases need to be studied in which maximum tolerated doses are used early in the course of the disease before a final decision can be made.

Miliary Tuberculosis with Meningitis—The single case reported by Anderson and Jewell was a failure in that the patient died

UNDULANT FEVER - BRUCELLA SUIIS

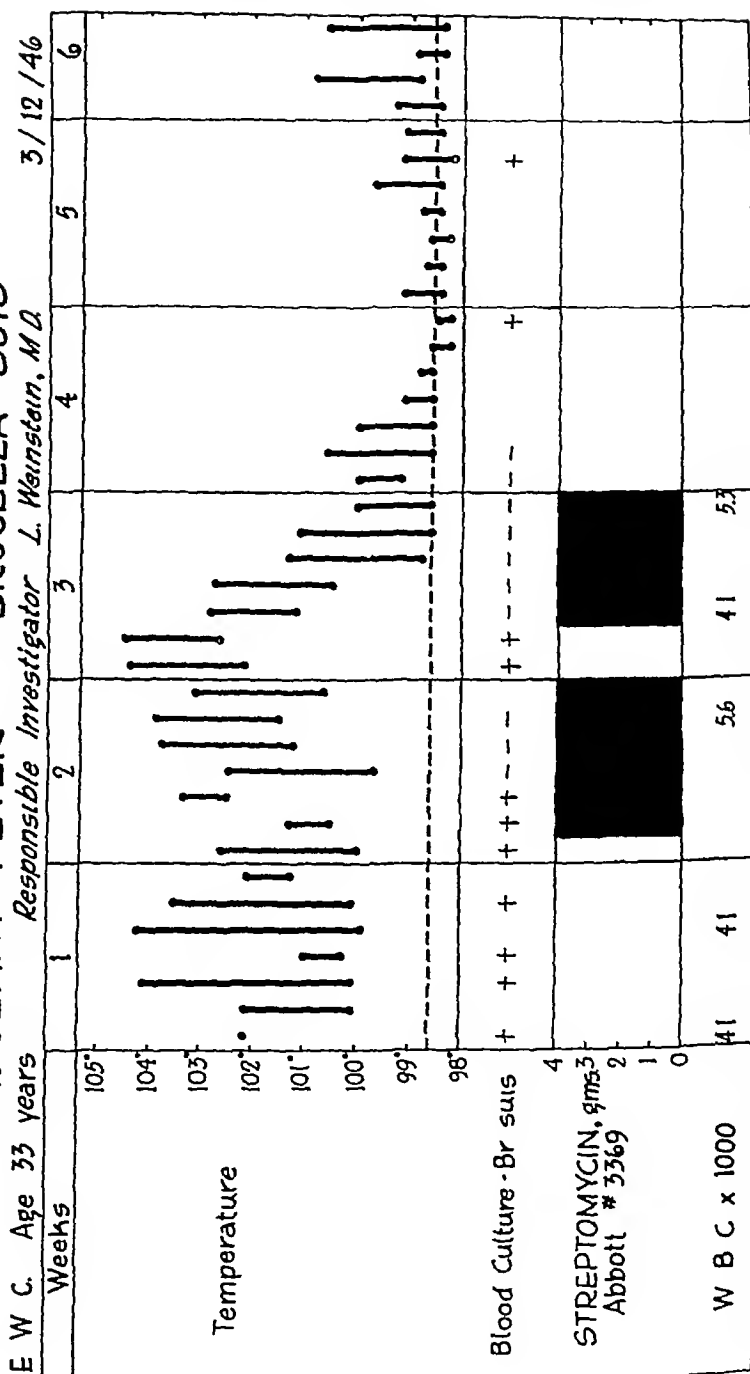


Fig 135 --Chart of patient with brucellosis, showing recurrence of bacteremia following discontinuing of streptomycin

SUMMARY AND CONCLUSIONS

From the study of results in fifty infections in which streptomycin was employed, the following statements are justified

1 Urinary tract infections due to some of the gram negative bacilli which are resistant to the sulfonamides may be influenced favorably by streptomycin. The various factors which must be taken into account are the type of infecting organism, the presence or absence of obstructive lesions or foreign bodies in the urinary tract, the sensitivity of the microorganisms, the reaction of the urine and the dosage of streptomycin.

2 *Bacillus proteus*, *Aerobacter aerogenes*, *Escherichia coli* and *Hemophilus influenzae* infections are more susceptible to the action of streptomycin than *Pseudomonas aeruginosa* and *Salmonella* infections.

3 Acquired resistance to streptomycin *in vivo* is a common feature of treatment, but clinical improvement may occur without sterilization of the urine.

4 Streptomycin was an effective therapeutic agent in *Hemophilus influenzae* meningitis when administered intramuscularly as well as intrathecally. Bacteremia was commonly cleared within twenty-four to forty-eight hours and the cerebrospinal fluid was sterilized within a similar period of time. It is recommended that intramuscular treatment be continued for three to four days and that intrathecal treatment be continued for at least seven days. The dosage should be 25 to 50 mg per pound of body weight intramuscularly in divided doses every three hours and 25 mg once or twice daily intrathecally.

5 In patients with pyocyanus sepsis, it is possible to clear the blood of organisms in some cases, but in others the resistance of the organism is so great that an adequate amount of streptomycin cannot be given. Urinary tract infections due to this organism may be extremely resistant.

6 *Salmonella* infections have been resistant to treatment.

7 Too few instances of typhoid fever and brucellosis have been studied to permit any conclusions. It would appear, however, that the effects of streptomycin are not striking in altering the course of either disease.

POSTWAR TROPICAL DISEASES IN THE UNITED STATES

GEORGE CHEEVER SHATTUCK, M D *

MALARIA

Species and Strains of Plasmodia.—Four species of malaria parasites are recognized today. Of these species only two are important in the United States, namely, *Plasmodium falciparum* and *P. vivax*. Strains or races of *P. vivax* differ much in virulence and in their response to treatment. The strains of *P. vivax* which have been long established in the United States cause a comparatively mild form of malaria which is relatively responsive to treatment. On the other hand, some of the strains of *P. vivax* now being imported from the Pacific islands can cause severe forms of malaria which are very persistent. Different strains of *P. vivax* are morphologically indistinguishable. Nearly all of the cases of malaria in service men who have returned to the United States are caused by *P. vivax*.

Vivax or Benign Tertian Malaria.—The usual course of vivax malaria in service men returned to the United States from islands in the Pacific was studied by Noe Jr, Greene Jr and Cheney (1946) in a series of patients who were not receiving specific treatment. They divided the course of the disease into three phases, (1) initial, (2) intermediate and (3) late or terminal.

The *initial phase* of a primary or first attack of vivax malaria does not begin with a chill and the temperature curve does not show tertian periodicity. Fever comes on insidiously and increases gradually. At first the temperature is continuous, but after a few days there are well marked daily remissions. The fever in the initial phase is accompanied by malaise such as is associated with the onset of many other febrile diseases. After about ten days, tertian periodicity supervenes and the onset of the febrile paroxysms is usually accompanied by chills. A spontaneous remission of the primary attack may be expected after two or more weeks.

The *intermediate phase* of vivax malaria is characterized by a series of relapses which begin abruptly with a sharp rise of temperature and a chill. The first relapse is likely to occur within from ten to twenty-one days. Subsequent relapses generally appear at longer intervals. The symptoms tend gradually to become less severe. According to Noe Jr and collaborators (1946), the duration of fever in relapses of Pacific malaria varies from one day to three months. The average duration in 113 of their untreated cases was 5.47 days. In the intervals be-

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tween relapses, there was more or less malaise, headache, or generalized pain. Occasionally a slight rise of temperature occurred. Relapses were few or many. The intervals between relapses were very variable in patients who did not receive specific therapy.

The symptoms which may appear during the intervals between attacks of vivax malaria have been described by Zeligs (1945). He attributed asthenia, in many instances, to causes other than malaria, such as combat fatigue, amebiasis or hookworm disease. Periodic headache, mild or severe, was a common symptom. The headaches were seldom of the migrainous or psychogenic type, they did not yield to the usual headache remedies, and they might continue for many months. As a rule, the headaches were bifrontal, worse on arising in the morning, and tending to wear off during the day. They were associated with disinclination to exertion, intolerance to a hot sun, and general inefficiency. There were no significant changes in the cerebrospinal fluid. More or less anemia usually developed.

In the *terminal phase* of vivax malaria, symptoms are slight or absent. Relapses, if they occur at all, appear at long intervals and are of brief duration. It is generally believed now that, in the absence of reinfection, vivax malaria seldom continues for more than three years and that spontaneously developing immunity will ultimately cure most cases. Even when specific therapy has been administered, the immune reaction seems to be an important, if not an essential, factor in the cure of vivax malaria.

Effects of Suppressive Medication.—The taking of quinacrine (atabrine) regularly in suppressive dosage does not prevent vivax infection because this drug is ineffective against the earlier stages of the parasite. Within a few weeks or months after suppressive medication has been discontinued, a persisting vivax infection is likely to cause an attack of fever. The primary attack is as described above. In subsequent attacks, the familiar malarial paroxysms occur. Varied and atypical symptoms are said to be common in persons who have been taking suppressive medication at irregular intervals. Headache or pain in various parts of the body may simulate other diseases.

Effects of Treatment.—Therapeutic doses of quinacrine usually control the fever in vivax malaria within three days. When attacks are treated promptly with quinacrine or with quinine, certain Pacific strains of malaria tend to recur regularly at intervals of about a month. The more resistant cases which have tended to accumulate in the hospitals in this country may have from twenty to thirty relapses. Noe Jr and collaborators (1946) believed that the striking uniformity of interval between relapses in treated cases is caused in some way by the treatment. They suspected that the course of the disease might be shortened by withholding treatment but they considered such a course impracticable.

Diagnosis—The clinical diagnosis of atypical forms of vivax malaria may be difficult even for one who is familiar with the disease. Evidence of possible exposure to malarial infection is important. When two series of vivax parasites are sporulating on alternate days, three paroxysms of fever occur daily. In the intervals, the temperature falls below the normal level. Some of the uncommon forms have been described by Most and Hayman Jr (1946). A primary attack may be delayed for many months by continued suppressive medication. Thick blood smears made twice daily may be negative for from two to five days even in the presence of high fever and daily chills. When parasites first appear, they may be few, whereas, during a relapse, they are likely to be numerous and may be found at the first examination.

Acute attacks of vivax malaria are often associated with gastrointestinal symptoms and these symptoms occasionally precede the febrile paroxysm by a day or two. The abdominal symptoms may be severe enough to suggest appendicitis, intestinal obstruction, or acute cholecystitis. In such cases the pain may be limited to the lower abdomen and there may be diffuse tenderness but there is no involuntary spasm, and rectal examination shows no localized sensitiveness. Usually the white count is normal or low, but it can be considerably increased.

Cerebral manifestations, when they occur in vivax malaria, are due probably to some pre-existing cause. Urticaria may precede or accompany an attack of vivax malaria, and upper respiratory symptoms are common, especially in winter. When there is a chill and a pain in the chest, accompanied by rales, one may mistake pneumonia for malaria, or vice versa.

Until a positive diagnosis has been made, unexplained fever or other symptoms of possible malarial origin in a returned service man, should not ordinarily be treated with antimalarials, sulfonamides, or other specific drugs.

Falciparum Malaria.—The cerebral, the circulatory and the abdominal manifestations of falciparum malaria are well known. Renal and other manifestations in great variety can occur. Alarming symptoms may develop without warning.

Suppressive Therapy—Ordinarily, so long as quinacrine is being taken daily in suppressive dosage, both vivax and falciparum infections are held in abeyance. It is believed that falciparum infections are often cured even by this small dosage of quinacrine. Vivax infections, on the other hand, are seldom if ever cured by suppressive medication.

Curative Therapy—Cases of falciparum malaria should be recognized and treated promptly because dangerous symptoms may appear suddenly. An acute attack of falciparum or of vivax malaria yields promptly to quinacrine or to quinine when properly administered in adequate dosage. Falciparum malaria may produce a few relapses but specific therapy soon eradicates the infection. Vivax malaria may re-

lapse again and again regardless of the method of treatment. Some of the Pacific strains of vivax are very persistent indeed

Apparently, neither quinacrine nor quinine can eradicate a virulent vivax infection until the action of the drug has been supplemented by increased immunological resistance. The development of immunological resistance is gradual. Prompt treatment of every acute attack may tend to delay the development of immunity but frequently repeated or prolonged attacks of fever may exert a harmful effect by causing debility and by lowering resistance. On the whole, it seems advisable to employ specific therapy for the control of distressing symptoms and to endeavor to enhance resistance to the disease by doing whatever is possible to improve the general condition of the patient. Concomitant parasitic or other infections should be looked for and treated appropriately when found.

Because quinacrine in average dosage is not promptly effective in acute malaria, larger dosage should be prescribed at first. This procedure is not necessary when quinine is employed because it acts promptly in average dosage.

The oral dosage of quinacrine which was recommended in July 1944 for the United States Army was quinacrine 0.2 gm (3 grains) and sodium bicarbonate 10 gm. (15 grains) with 200 to 300 cubic centimeters of water every six hours for five doses. Thereafter, quinacrine 0.1 gm. (1.5 grains) three times daily after meals for six days (War Dept. Tech. Bull. 1944).

When a proved case of malaria does not respond promptly to oral medication it may be because the drug is not being well absorbed. At such times medication should be parenteral. Other indications for parenteral therapy are well known. Certain preparations of quinacrine or of quinine are suitable for intramuscular use but, for intravenous injections only quinine is recommended. In order to avoid toxic effects on the circulation quinine should be administered in about 200 cc. of normal saline and the injection should be given very slowly.

Prevention of Relapse.—No drug which is well known can be counted upon to prevent relapse in vivax malaria but relapse can be postponed by suppressive medication. Recent studies indicate that plasmochin used in conjunction with quinacrine has some effect in preventing relapse. Because the margin between therapeutic and toxic dosage is narrow plasmochin should be used with caution and only when the patient is under close supervision.

Neoarsphenamine or other arsenicals may be beneficial in vivax malaria but they have little effect upon falciparum infections. Occasionally a dose or two of neoarsphenamine is followed by complete cure of a persistent vivax infection but tests by the United States Army show that this result is unusual. Neoarsphenamine is most likely to be useful in debilitated cases of chronic malaria.

New Drugs.—*Thiobismol* will promptly check malarial fever but the effect is too transient to be of much value

The Board for the Coordination of Malarial Studies (1946) has published a brief report recently on some of the newer antimalarials

In the 4-aminoquinoline series, several members are thought to be of special value In this group, *chloroquine* or SN 7618, 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, is an effective suppressive when administered once weekly It will abruptly terminate an attack of vivax malaria and it well may have a similar effect on falciparum malaria when administered for only one or two days The toxicity is lower than that of quinacrine

Other compounds of the same group have not yet reached the stage of field trial Some of the *8-aminoquinolines* are under investigation These drugs are chemically related to plasmochin

Paludrine (ICI) which appears to be the most promising of the new British antimalarial drugs, was produced by the Imperial Chemical Industries, Ltd An unsigned note upon the use of paludrine in human malaria (*Lancet* 1945) said that paludrine is at least as effective as quinacrine (mepacrine British) in the treatment of falciparum or vivax malaria It causes no staining of the skin and no toxic manifestations have followed its use as yet in dosage which is far in excess of that required for therapeutic effect It is believed that paludrine can be produced more cheaply than mepacrine Use of the drug is still in the experimental stage, and paludrine is not yet available for sale

A series of reports from the Imperial Chemical Industries Limited (1945), on several of their new antimalarial drugs, has just appeared These reports are by various authors With regard to paludrine as a therapeutic agent in human malaria, the reports are in accord with the note which appeared in the *Lancet* (1945)

General care and symptomatic treatment should not be neglected in malaria Rest in bed should be insisted upon when there is fever and, in primary or early attacks of malaria, the patient should remain in bed for several days after abatement of the fever

THE LEISHMANIASSES

In years past, an occasional case of oriental sore, caused by *Leishmania tropica*, or of visceral leishmaniasis (kala-azar), caused by *L. donovani*, has been recognized in a recent immigrant to this country The typical oriental sore is a localized subacute or chronic inflammatory lesion which is common in parts of the Near East and of India The *visceral form* of the disease is characterized by enlargement of the spleen and usually of the liver, as well as by irregular fever The course of the disease is subacute or chronic Visceral leishmaniasis is common, especially among children, along the Mediterranean littoral

In adults, the disease is very prevalent in Bengal, in Assam, and in the great river valleys of China

A few cases of visceral leishmaniasis have been recognized in service men from North Africa and Italy

The disease is especially to be distinguished from malaria. In the earlier stages of the infection, the patient may appear to be well, even when fever is present. Emaciation of the limbs and swelling of the abdomen appear later

Because the incubation period of visceral leishmaniasis may be prolonged, it seems possible that a few cases might develop in men who have been discharged from the Services

The *diagnosis* is made by excluding malaria and other causes of splenomegaly and by demonstrating *Leishmania* in material obtained by spleen puncture or sternal puncture

Treatment is by intravenous injections of potassium or sodium antimonyl tartrate or by the less toxic pentavalent antimonials Neostibosan has proved satisfactory

AMEBIASIS

Incidence—Probably 10 per cent or more of all the inhabitants of the United States are infected with *Endamoeba histolytica*. Some estimates have put the figure at 20 per cent. Among one thousand unselected military returnees *E. histolytica* was found in 16.8 per cent (Marion and Sweetser 1946)

Symptomatology—In the great majority of cases of amebiasis, symptoms are absent or mild and vague. A considerable proportion of cases of amebiasis have chronic constipation which is interrupted occasionally by attacks of diarrhea. The occurrence of acute dysentery or of liver abscess is exceptional. Even when there is extensive chronic ulceration of the large intestine there may be few or no gastrointestinal manifestations. In other instances, the symptomatology is that of chronic ulcerative colitis. In the majority of cases of this type, secondary bacterial infection of the ulcers is an important factor in the production of the symptomatology

Severe intestinal hemorrhage, perforation of the bowel or liver abscess may develop in an apparently cured or previously unrecognized case of amebiasis. Appendiceal inflammation of various grades or tenderness caused by cecal ulceration may lead to appendectomy. Unless the amebic infection has been recognized and treated appropriately, the operative results are likely to be unsatisfactory

Diagnosis—The very varied nature of the symptomatology of amebiasis points to the necessity for confirmation of the diagnosis by demonstrating the presence of *E. histolytica*. To recognize this organism in acute cases of amebic dysentery may not be difficult but an inade

quately trained microscopist may fail to recognize *E. histolytica* when it is present or may mistake something else for this organism. The laboratory diagnosis of amebiasis should be entrusted only to a protozoologist or to one who has been well trained for this highly specialized work. The necessity for such special training should be recognized generally. The value of the complement fixation test for diagnosis is restricted by the difficulty of obtaining a satisfactory antigen.

An amebic ulcer may become cancerous or an amebic granuloma may be mistaken for cancer.

Amebiasis can be associated with other diseases. The presence of cysts of *E. histolytica* in the feces does not prove that this organism is the cause of symptoms.

When the presence of liver abscess is suspected, and when the abscess cannot be localized by ordinary means, the employment of thorotrast should be considered.

Treatment—The most effective drug for the control of acute amebiasis is emetine and this is the only drug which acts against amebae in the liver. Unfortunately, toxic effects, of a potentially serious character, are so often caused by emetine that this drug should be administered only to patients who are being kept in bed and who are under close observation.

A course of daily injections of emetine hydrochloride will usually control the severe symptoms in a case of uncomplicated amebiasis within from three to five days. A longer course of this drug will seldom accomplish more. To complete the cure, one or two courses of chiniofon, diodoquin, or carbarsone, should be prescribed at intervals. There is no unanimity of opinion regarding the relative value of these drugs. A significant number of incomplete cures with each of them have been reported. When one of them fails to cure, another may be tried. Any of them may cause toxic effects. Complete cure should be the objective in all cases of amebiasis, lest severe symptoms or complications supervene. After an apparent cure, the stools should be re-examined for *E. histolytica* at intervals of a few weeks, for six months.

In obstinate cases of intestinal or hepatic amebiasis in which secondary bacterial infection is believed to be an important factor, the use of antibacterial drugs, such as the sulfonamides or penicillin, should be considered. It is unlikely that either of these drugs would have any effect upon the ameba.

Little information has as yet been published on the use of sulfonamides or of penicillin to combat secondary bacterial infection in amebiasis. Marked benefit has been reported by Hargreaves (1945) in severe amebic colitis following the administration of sulfasuxidine by mouth in conjunction with penicillin intramuscularly and he has seen marked improvement after the use of penicillin alone. A standard course of anti-amebic treatment was given after completion of the

antibacterial therapy Willmore (1945) had similar experiences with penicillin

The treatment of liver abscess with and without surgical intervention has been ably discussed by Ochsner and DeBakey (1943), and Alport and Ghaliougui (1939) treated five cases of liver abscess by aspiration and medication Noth and Hirshfeld (1944) reported a case of amebic abscess of the liver infected with streptococci which yielded to emetine aspiration and injection of penicillin into the abscess cavity

SCHISTOSOMIASIS

The more important schistosomes of man are *Schistosoma haematobium*, which attacks especially the genitourinary tract, and *S. mansoni* and *S. japonicum*, which are essentially parasites of the lower bowel

A small number of cases of infection with *S. haematobium* are said to have occurred in personnel of our military forces in North Africa and in Liberia. A considerable number of infections with *S. japonicum* were contracted in some of the Pacific islands and especially in the Philippines *Schistosoma mansoni* is common in parts of Africa, of northern South America and of the West Indies There are important foci of this disease in Puerto Rico

Presumably, most of the schistosome infections in service men will have been recognized and cured before infected individuals are discharged but a few mild and unrecognized or incompletely cured cases may, perhaps, come to the attention of civilian practitioners It is important that this disease be treated before irreparable damage can occur Cerebral manifestations occur, rarely as a result of ova lodging in the brain Eosinophilia is rather constantly present.

Diagnosis—The ova of *S. haematobium* are to be sought for in the urine and those of *S. mansoni* and of *S. japonicum* in the feces The first has a terminal spine, the second a lateral spine, and usually the last has a knob on the side which is not clearly visible Certain concentration methods are recommended when ova are scarce The cystoscope may show the characteristic lesions of *S. haematobium* in the bladder and the proctoscope or sigmoidoscope may facilitate the diagnosis of infection with either of the other parasites Rectal biopsy has been used with pronounced success in the diagnosis of early or slight lesions of the rectal mucosa caused by *S. mansoni* when ova could not be found in the feces. It is necessary only to remove a very small bit of mucous membrane and this procedure has proved harmless. The same procedure may be equally valuable for the recognition of *S. japonicum*

Treatment—The classical treatment for schistosomiasis is a prolonged course of intravenous injections of sodium or potassium antimonyl tartrate The lower toxicity of fudrin (foudin neoantimonan or stibophan) and the fact that this drug is suitable for intramuscular

injection, have led to its use as a substitute for the tartrates. Both of these antimonials are trivalent and both are more effective in schistosomiasis than are the quinquivalent antimonials. A single course of treatment either with antimonyl tartrate or with fuadin does not cure all cases. The proportion of complete cures reported by different authors after a first course of treatment in early cases varies widely but it is believed that early treatment will at least prevent the development of severe sequelae.

Fuller information about schistosomiasis in service men has been published recently and additional information as to treatment is expected to appear soon.

BANCROFTIAN FILIARIASIS

Cases of real or supposed infection with bancroftian filariasis contracted in the South Pacific have already attracted so much attention that it is needless to say much about the condition.

Microfilariae have very rarely been found in the blood in cases of bancroftian filariasis in service men from the Pacific. Biopsy is not ordinarily advisable and skin tests are of doubtful value for diagnosis (Augustine and Lherisson, 1946). Usually the diagnosis has been based, (1) upon possible exposure determined with reference to the distribution of the parasite, and (2) upon the presence of rather characteristic symptoms. Skin tests, when positive, are of doubtful significance (Augustine and Lherisson, 1946).

Because of the complications which may be associated with this form of filariasis, and because few cases of the early manifestations of the disease had been followed for any length of time, it was feared at first that our service men who became infected might subsequently develop large lymph scrotum or elephantiasis. The psychic trauma to the men themselves who had seen these things was often the most serious symptom requiring treatment. In dealing with these patients, reassurance may be of the first importance. It can now be said with confidence that most of the men who had more or less characteristic symptoms of early filariasis have recovered, that sterility is not to be feared, and that if lesions of any consequence have occurred, they have developed in not more than a fraction of one per cent of the cases. No very effective method of chemotherapy has been reported. Theoretically, a drug which is capable of quickly killing all adult filariae in the body might produce harmful inflammatory reactions because it is believed that the living parasite causes less local inflammation than the dead parasite.

ANCYLOSTOMIASIS

The common hookworm of the United States, *Necator americanus*, was introduced from tropical Africa. That of North Africa and other Mediterranean countries, is *Ancylostoma duodenale*. Both species occur

throughout the Orient and the South Pacific Islands. The more resistant of the two to treatment is *Ancylostoma*. As a rule, a single course of treatment with tetrachlorethylene will remove a large proportion of the worms of either species but complete eradication of the parasites may be difficult.

Hookworm disease is ordinarily caused by a large worm burden, resulting from repeated reinfection. In addition to expelling the worms, it may be necessary to improve the diet and to treat the anemia with iron. Cases of light infection are usually asymptomatic and the worms gradually die off if reinfection does not occur.

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VIRUS DISEASE FROM THE CLINICAL POINT OF VIEW

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Virus diseases, such as mumps and smallpox, have been known for centuries. Excellent descriptions of some of the common ones were written one hundred years ago. It was not, however, until the end of the last century that a virus was discovered. During the past fifty years specific viruses have been isolated and identified as the causative factors in a large number of diseases of plants, animals and man, and new viruses are constantly being found. Those affecting man constitute a shorter list than those affecting either animals or plants.

One must realize that rapid advances are being made which constantly shed new light in this field of study. Surrounding the stable facts of virology is a mass of knowledge which is in a constant state of flux, with here and there whirlpools of agitation created by speculative hypotheses promulgated alike by the clinician, epidemiologist and laboratory worker. This article is devoted to some of the broader aspects of virology that concern the clinician and to a few concrete examples.

PLACE OF THE VIRUS AMONG THE INFECTIVE AGENTS OF DISEASE

Protozoa
Spirochaeta
Fungi
Bacteria
Rickettsia
Viruses †

As etiologic agents of disease, viruses are midget parasites, too small to be seen with the ordinary microscope, and in general are capable of passing through a standard filter which prevents the passage of bacteria. But small as these pathogenic viruses are, they vary in diameter from 225 millimicrons (vaccinia) to 11 millimicrons (influenza). So far as is known, a virus can multiply only in living susceptible cells, and for the most part viruses are extraordinarily selective in the cells they multiply in. But there is much variation in the degree of selective affinity. The viruses of rabies and of poliomyelitis multiply only in cells

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† Bacteriophage which is responsible for the phenomenon of transmissible lysis of bacteria, is in many ways analogous to virus multiplication of the phage occurring only in the presence of the actively growing bacteria.¹

of the nervous system, whereas the virus of mumps multiplies in many different glandular tissues, as well as in cells of the nervous system. The virus of yellow fever is found in enormous concentration in the blood during the three days of the height of the disease, while the virus of influenza multiplies in the epithelial cells of the upper and lower respiratory tract and is never found in the blood at any stage of the disease. Thus the clinician is impressed by the wide variety in the size of the pathogenic viruses of man, by the variety of their selective affinity, and by the fact that the virus of one disease is found in the blood, whereas the virus of another is apparently confined to its area of activity.

We must keep in mind that some of the virus diseases which attack mankind are essentially diseases of animals and attack man only occasionally, as when a mad dog bites a man, or when a man tends a parrot sick with psittacosis. Finally, some virus diseases may be entirely confined to man so far as is known, among which are those common diseases usually acquired in childhood—mumps, measles and chickenpox.

VIRUS DISEASES PATHOGENIC TO MAN

Common wart (verruca)
 Cow wart
 Molluscum contagiosum
 Common cold
 Influenza
 Atypical pneumonia (virus pneumonitis)
 Feline pneumonitis (cat fever)
 Measles (rubeola)
 German measles (rubella)
 Chickenpox (varicella)
 Smallpox (variola)
 Varioloid (modified by acquired partial immunity through vaccination)
 Alastrim (modified by natural partial immunity)
 Vaccinia (cowpox)
 Erythema exanthema
 Mumps
 Foot and mouth disease
 Vesicular stomatitis
 Herpes simplex or labialis (cold sore or fever sore)
 Herpes zoster (shingles)
 Lymphocytic fever
 Infectious hepatitis
 Rift Valley fever (enzootic hepatitis)
 Dengue fever
 Yellow fever
 Pappataci fever (sandfly fever, phlebotomous fever)
 Lymphocytic choriomeningitis
 Louping ill (Russian spring encephalitis, Australian X disease)
 Japanese B encephalitis
 St. Louis encephalitis (epidemic encephalitis)
 Western strain equine encephalomyelitis

Eastern strain equine encephalomyelitis
 Rabies
 Pseudorabies
 Poliomyelitis (infantile paralysis)

DISEASES DUE TO SEROLOGICALLY RELATED AGENTS OF VIRUS CHARACTER

Some strains susceptible to penicillin or sulfa drugs*

Ornithoses (psittacosis parrot fever parakeet fever Also from pigeon canary and many other birds of bright plumage)

Trachoma

Inclusion conjunctivitis

Lymphogranuloma venereum

DISEASES CLINICALLY SUGGESTIVE OF VIRUS ORIGIN BUT FROM WHICH NO VIRUS HAS BEEN ISOLATED

Infectious mononucleosis

Infectious polyneuritis (Guillain Barré syndrome)

Roseola infantum (exanthema subitum)

Erythema infectiosum

NATURE AND ORIGIN OF VIRUS

This leads us to a consideration of the nature of a virus. The popular conception of the origin of a virus is that it represents a retrograde evolution of a living cell whereby only that part of the nucleus remains "degraded through long persistent parasitism. the irreducible minimum required to transmit the characters of the species"³ As pointed out by Rivers,⁴ however, "all viruses are not of necessity alike in nature." Thus he says "I am of the opinion that some viruses may be minute highly parasitic microorganisms the midguts of the microbial world, capable of reproduction only within susceptible host cells that others may represent forms of life more or less unfamiliar to us and that still others may be fabrications of their host cells aided by the process of autocatalysis." A virus is comparable to a hypothetical isolated gene. It "never arises *de novo*, but like any other organism it derives by genetic descent from a similar particle," and in its turn reproduces itself under appropriate conditions.¹

The virus of tobacco-mosaic can be obtained in the form of crystalline protein which retains its infectious properties. Since this discovery by Stanley,⁵ twelve different viruses affecting plants and animals have been obtained in this crystalline form. This crystallization of a virus has raised the question of whether or not such a substance is inanimate. It is difficult, however to think of a substance as inanimate which is capable of reproducing itself in the cells of its host.

The virus in the course of its existence produces certain serological phenomena similar to those of other infectious agents, such as comple-

* There is some question as to whether some or all of this group are really viruses, but the psittacoses appear to fulfill the laboratory requirements.²

ment fixation, agglutination, precipitation and neutralization, which, as Rivers⁴ reminds us, "while interesting, may not be directly responsible for the immune state of the host"

TRANSIENT FALSE POSITIVE HINTON REACTIONS IN VIRUS DISEASE

At this point it is well to mention that many diseases may produce a transient false positive Hinton reaction for syphilis. Among the virus diseases in which this phenomenon is found are chickenpox, smallpox, vaccinia, measles, mumps, lymphogranuloma venereum, infectious hepatitis, atypical pneumonia, and infectious mononucleosis.⁶

ATTENUATION OF VIRUS FOR VACCINATION

A characteristic of viruses—but not necessarily of all—is that they are capable of undergoing mutation through environmental factors. This brings up the theory of attenuation, which is the basis of our preventive vaccines. It is generally believed that the virus of cowpox came into existence as a result of infection of the cow with smallpox virus.⁵ In other words, the smallpox virus underwent a mutation in the cow, and when it again entered man it was in an attenuated state giving rise to the milder disease, vaccinia.

Vaccinia is not a purely local infection, although it may appear so in comparison to smallpox. Indeed, the vaccine virus has been shown to be present in the pharynx soon after a cutaneous "take."⁷

Vaccination against smallpox by the intracutaneous method may be performed as a preventive in case of exposure to smallpox, because the incubation period of vaccinia is only four or five days, whereas that of smallpox is fourteen to twenty-one days. Vaccination at the first birthday is better than vaccination when the child enters school, as post-vaccinal encephalomyelitis, though it is exceedingly rare, is even less frequent at the earlier age.

Generalized vaccinia is as serious as smallpox. Fortunately, it is rare. It is most apt to occur in the presence of a generalized eruption such as chronic eczema. Not only should individuals with generalized eczema not be vaccinated, but they should be isolated from children that have just been vaccinated, as an eczematous child may contract generalized vaccinia by exposure to a recently vaccinated individual.⁸

Jenner's discovery in 1798 of vaccinia as a preventive of smallpox was followed by Pasteur's mutation of the virus of rabies through inoculation into a rabbit under the *dura mater*. The "street virus" is the virus obtained from the mad dog. When this virus is inoculated into rabbits and then transferred from rabbit to rabbit, it undergoes a mutation and finally is "fixed," losing its virulence for dog and man. In this form it is used as a preventive both in the inoculation of healthy dogs and in the treatment of a person known to have been bitten by a rabid animal. The dangers of administering this fixed virus are that

healthy dogs so inoculated may develop actual rabies, and man may develop a post rabies vaccination encephalomyelitis. It is, therefore, advisable not to institute Pasteur treatment to an individual bitten by a dog that is still living fourteen days from the time of the biting. For further particulars, consult your State Department of Health by telephone.

In 1930 Theiler reported that the virus of yellow fever could be attenuated through passage from mouse brain to mouse brain. Eventually a strain known as 17D was produced which is so modified as to be a safe preventive against yellow fever. This was given to over four million people in one year.

Except those used for smallpox, rabies and yellow fever there are no well established vaccines against virus diseases. The basis of all vaccines against virus disease must be a living attenuated virus in susceptible host cells. The chorioallantois of the embryo chick has been found useful in making up vaccinia virus. It has also been used for growing the other viruses such as measles, but the problem is to attenuate such viruses first or to effect it by this process itself. Attempts have been made to attenuate poliomyelitis virus, but the material proved to be either inert or, if active, induced true poliomyelitis. Recently a vaccine containing both influenza A and B virus has been developed by Thomas Francis and is now in use by the United States Army. The results at present appear to be encouraging. Vaccines for the common cold have been greatly in demand, but these so-called catarrhal vaccines are made up of bacteria commonly inhabiting the upper respiratory tract and do not contain the virus of the common cold. They are valuable therefore against these bacteria, but even so their worth is still questionable in the light of controlled statistical evidence.⁹

IMMUNITY TO VIRUS DISEASE

Immunity to virus disease is a complicated subject. There is a natural immunity in some individuals which may be transient or permanent. It is well known that there is a relative immunity to measles in the first two to four months of life. This is so regardless of the mother's own immunity at the time the child is born, and whether or not the baby is breast fed. I have seen a two months old infant which was allowed to continue at the breast of its mother during the latter's attack of full blown measles without showing any signs of the disease. Rolleston and Ronaldson¹⁰ state that "In no case, therefore, should the existence of measles in the mother form a contraindication to suckling as if the infant is susceptible infection will already have taken place by the time the measles have been diagnosed in the mother."

In the case alluded to the mother had never had measles, although there had been ample exposure, for she had slept as a child in the same bed with her sister during her sister's attack. On reaching mother

hood she contracted the disease from her older child. This curious natural immunity, with a breakdown in the barriers during parenthood, is also observed in chickenpox. Congenital measles and chickenpox have been recorded, but are generally mild.

Immunity to virus disease may be acquired by a subminimal infection, by an attack so light as to go unrecognized, by a well recognized attack, or, as in smallpox and yellow fever, by vaccination with an attenuated virus, which constitutes a mild attack. In smallpox there are three well known clinical varieties of the disease: variola vera, or true smallpox, varioloid, which is a mild form due to partial immunity gained by previous vaccination, and alastrim, also a mild form which is thought to be due either to a natural partial immunity or to an attenuated strain of human smallpox virus.

An idea is commonly held that in an attack of mumps involving only one parotid the subsequent immunity is less than if both parotids had been involved. This erroneous conception is based on the idea that this disease is purely local. As a matter of fact, the cytotropic activity of the mumps virus displays itself in many glandular organs, but with a marked selective affinity for the parotid. In addition, the virus of mumps has pronounced neurotropic properties. In smallpox, vaccinia, chickenpox, measles and yellow fever the virus is widely distributed throughout the body, giving rise to visceral lesions, and here again, as in mumps, a permanent immunity is acquired.

Inasmuch as acquired immunity is derived from an actual infection, the established forces of resistance are retained by some mechanism which prevents reinfection. In some virus diseases this acquired immunity is permanent, while in virus diseases of the upper respiratory tract, such as the common cold and influenza, the immunity is temporary. Rivers⁴ has suggested that the type of tissue involved may be responsible for this variation in the duration of immunity. The virus in infections of the respiratory tract invades the cells of superficial tissues. These tissues in themselves are but temporary and are rather rapidly replaced through desquamation. All this suggests that immunity may be dependent on the virus remaining in the host after the attack. One has to assume that the virus remains somewhere in the host in a state of latent inactivity, migrating with the death of the cell to a neighboring cell, but continuing in a hibernating state. In the course of this quiescent existence it does no damage to the cell, and the virus and the cell live together peacefully. The virus, however, by catalysis might stimulate antibody formation in the surroundings, and these antibodies, circulating in the host, could maintain immunity. This is all speculative but is given support from the results of plant experiments by Kunkel, as quoted by Rivers.⁴ It seems that periwinkles may become infected with a virus disease known as aster yellows. After an attack, a plant is immune to further infection, but if the plant is sub-

jected to heat which destroys the virus without injury to the plant, then it loses its immunity and may again become infected.

A patient of mine had chickenpox at the age of eight and enjoyed an immunity to later exposures. During her first year in college she had a definite exposure to this disease through a classmate, but escaped. The following year with no intervening illness and while in apparently good health, she contracted chickenpox from another student. It is possible that during the last year the virus of chickenpox died out within her and with its disappearance antibody production ceased. Passive immunity has been covered in the January 1946 issue of *Medical Clinics of North America* ²

EPIDEMIOLOGY OF VIRUS DISEASES

Period of Infectivity—The spread of virus disease is accomplished by various methods. When the infection is in the upper respiratory tract the spread is either direct, as in kissing or through the hand if it is in constant contact with the mouth, where the saliva may be teeming with virus as in mumps or with a running nose, as in measles and the common cold. The viruses of infections of the upper respiratory tract are easily forced into the surrounding air especially if a cough is present, though coughing is unnecessary for air borne infections. Thus it is that smallpox, chickenpox, measles and mumps may be air borne from the respiratory passage of the donor to the recipient. All these diseases are highly infectious in the prodromal period even in the absence of prodromal symptoms. The mysteries of the spread of chickenpox become clearer when we appreciate that this disease is spread for as long as four days prior to the eruption and that its infectivity ceases after the fifth day regardless of the presence of vesicles or scabs ¹¹. This does not mean that the lesions in themselves are not infectious. The fresh skin lesions undoubtedly constitute a factor in the spread, but these are not by any means the only factor. Isolation for the duration of the scabs is a questionable procedure.

The mumps virus has never been found later than seventy six hours after the onset of the disease, but it is unknown whether the salivary glands continue to secrete the virus in the presence of encephalitis, pancreatitis or orchitis. Measles is contagious for several days prior to the eruption, and only during the height of the eruption. In contrast to chickenpox, smallpox is infectious for the duration of the active eruption which may be several weeks, as the virus persists here in the crusts and may be carried in fomites.

Air borne and Contact Infection—The question of how far air borne infections are carried depends on whether the air is still or whether there is a brisk current from the patient's face to that of the recipient. The dose of virus received is also an important item. Coughing and sneezing may cause the air to be heavily laden. Most viruses

are destroyed by ultraviolet rays. The effectiveness of glycol preparations is dependent on a high humidity of the air.

Too often the clinician lays undue stress on air-borne infection at the expense of contact infection. While it is true that the main value of a mask is in the protection it gives to the patient, this effectiveness is dependent on technic. The mother of an infant is told to wear a mask while caring for her infant, especially if the mother has a cold. But if the mother constantly brings her hand up to the virus-saturated mask and handles her own or the bottle nipple at the same time, she practically feeds virus to the baby. It is equally poor technic for a physician to don a mask, handle his patient, and at the same time constantly bring his hand up to the mask to adjust it. The mask should never be handled after it is adjusted any more than it is in surgery.

Contact infection by hand is an important factor. It is well to realize that soap and water are adequate to rid the hands of virus, and are always available in general practice and on hospital wards. Lymphogranuloma venereum is a venereal disease of human origin.^{12, 13}

Transmission of Virus by Animals and Insects—Rabies can be transmitted from the infected animal to man both by biting and by licking of an open skin wound. The mad dog dies, but the vampire bat of Trinidad may carry rabies in his saliva for five months and infect a sleeping native by licking an open sore. A person removing a common gray mouse from a trap may contract lymphocytic choriomeningitis, a disease due to a virus which is carried from generation to generation in mice in certain localities. The bed bug can also bring this disease from mouse to man. Man may contract psittacosis from cleaning the cage of a parrot or picking up a dead pigeon. Cow wart, foot and mouth disease of cattle, and vesicular stomatitis are spread more or less directly from the infected animal to man. Yellow fever, dengue, sandfly fever, louping ill and eastern and western equine encephalomyelitis have been proved to be carried to man by the bite of infected mosquitoes.¹⁴ Japanese B encephalitis is probably transmitted to man by a mosquito. Rift Valley fever and St. Louis encephalitis are thought to be carried to man by insect vectors, but as yet the vectors have not been established.¹⁵

Yellow fever is transferred from man to the mosquito only during the three or four days of the height of the disease when the blood is teeming with virus. Therefore, man does not serve as a carrier. The same applies to the monkey, but wild fowl of the jungle may possibly serve as carriers. Accidental infections of man have occurred in laboratory workers through handling potent virus.

PATHOLOGY OF VIRUS INFECTIONS

In the pathology of virus infections we have elementary or "nuclear inclusion bodies" in the lesions. These bodies represent the presence of

virus in the cell. They vary in numbers and character Van Royen and Illingsworth¹⁶ have utilized this factor in a rapid laboratory test to differentiate smallpox from chickenpox. Scrapings of the early lesions are stained by the Paschen method. In smallpox the preparation shows large numbers of elementary bodies whereas in chickenpox only a few are present.

Another characteristic of virus pathology is round cell or giant cell infiltration. These are found in the lesions of chickenpox and smallpox,¹⁷ and in the Koplik spots of measles.¹⁸ Endothelial cell proliferation and perivascular infiltration are also present. The corona or erythematous halo about the chickenpox lesion is much more striking than in the smallpox lesion. Where the activity of a virus produces vesiculation there is liquefaction of the epithelial cells with ballooning. As the fluid is absorbed, the coagulated fibrin and epithelial cells form a scab or crust. In chickenpox there is relatively little emigration of leukocytes, while in smallpox the lesion goes on to a pustule which frequently becomes contaminated with streptococci. An important feature of the malignant forms of the virus exanthemas is secondary blood infection. In the so-called purpuric forms of measles streptococcic or staphylococcic bacteremia is responsible for the severity of this condition, and streptococcic bacteremia is usually present in fatal smallpox. In marasmic infants chickenpox lesions may become enormous bullae as the result of streptococcic contamination and streptococcic pneumonia and bacteremia can occur in this disease.

A wide dispersion of visceral lesions is found in chickenpox, smallpox and measles. In mumps we may have involvement of many different glandular tissues as well as a benign meningoencephalitis, and the eye may suffer as well as the internal ear.¹⁹ Tomlinson²⁰ found in tonsils extracted in the pre-eruptive stage of chickenpox the same giant cell formation that is found in the tonsils in measles. Johnson²¹ found widespread visceral lesions in a patient with chickenpox who died on the third day. Areas of focal degeneration similar to those seen in the skin were present in the esophagus, pancreas, liver, renal pelvis, bladder and adrenal glands.

In the course of an attack of a virus disease, the virus enters the susceptible host cell and after an incubation period of quiescence suddenly bursts into activity and the irritation may destroy the cell. The resultant damage depends largely on the type of cell involved. In mumps the acinar cells in the parotid gland are readily replaced, and the gland is restored to normal without scarring. The superficial epithelial skin cell invaded in chickenpox is also restored without scarring, while the deeper cell invaded in smallpox leaves the characteristic pits with permanent scars. In poliomyelitis actual destruction of anterior horn cells leads to permanent paralysis.

In yellow fever the predominant lesion is a necrosis of the liver

Whether the virus actually multiplies in this organ, or whether the lesions are merely the result of the presence of the virus, is not yet known. Infectious hepatitis also destroys hepatic cells.

Lymphocytic Choriomeningitis.—Lymphocytic choriomeningitis presents several interesting features. The normal habitat of the virus is in the common gray mouse, often producing a paralysis of the hind legs. In the guinea pig it produces a highly fatal form of interstitial pneumonia. In man it gives rise to a fever on the sixth day that subsides, after which the patient is well for a week. Then he begins to have a chill, fever and headache, and shows signs of meningeal irritation due to involvement of the choroid plexus. The spinal fluid gives a cell count of from 50 to 1000 cells with 90 to 100 per cent lymphocytes. After a week the symptoms subside, and he recovers. At six weeks complement-fixing antibody appears in the blood, reaching its height in the eighth week. Sometimes the illness is protracted, and in rare instances a virulent strain is encountered which can cause the same disease found in the guinea pig, namely, a fatal interstitial pneumonia.

Encephalitis.—When a virus invades the encephalon, we may have all degrees of inflammation, depending on the virulence of the virus and the resistance of the host. The virus of vaccinia, measles, chickenpox and mumps may, under certain circumstances, break through the blood brain barrier and reach the encephalon. The encephalitis which follows varies greatly in its severity and is no way proportionate to the severity of the original disease itself. In measles, chickenpox and vaccinia we may have a severe encephalitis followed by personality changes.

Some degree of encephalitis, as evidenced by headache, fever and rigidity of the neck and spine, occurs in approximately 10 per cent of patients at the military age who have mumps. This encephalitis is almost invariably benign, and may precede, accompany or follow the parotitis. Indeed, encephalitis, like orchitis, may occur without any signs of salivary gland involvement. This is indistinguishable at the time by clinical and laboratory methods from nonparalytic poliomyelitis, but subsequently a rise in mumps antibody as revealed by the Enders²² method establishes the diagnosis of mumps encephalitis. The mildest form of human encephalitis occurs in mumps, where we may have a "latent encephalitis" so mild as to be determined only by means of the pleocytosis found at lumbar puncture. As many as 800 cells have been found in the spinal fluid with no clinical suggestion of meningeal irritation.¹⁰

Encephalomyelitis occurs exceedingly rarely in mumps. In fact, it is about as rare as in measles, the rate of which is approximately one in two thousand, including all age groups. In chickenpox it is also rare and in vaccinia even more rare. It thus becomes apparent that the virus of mumps is relatively more neurotropic, although definitely more be

nign in character, than the viruses of these other common diseases. This brings up the question as to whether these rare "postinfectious" encephalomyelitides may not represent the activation of some latent encephalomyelitic virus as a result of these common virus infections. This question can be answered only by an improvement in our laboratory diagnosis of virus encephalitides.

Other viruses are essentially neurotropic, such as the virus of rabies, eastern strain equine encephalomyelitis, poliomyelitis and the forms of lethargic encephalitis, the last mentioned being clinically indistinguishable from that seen occasionally in measles, chickenpox and vaccinia. Thus we have at one end the mildest form of encephalitis derived from the mumps virus and at the other end the severest forms which are usually fatal, as exhibited in rabies and eastern strain encephalomyelitis.

Herpes Simplex.—Herpes simplex (cold sore or fever sore) usually occurs on the lips but occasionally lesions are found on the skin, especially extending away from the lips and in rare instances on the cornea or genitalia. Frequently the primary infection is in the form of an aphthous stomatitis in childhood and persists through life. The virus was discovered by Gruter in 1912. Burnet¹ records the case of a woman who had never had cold sores and by test showed no antibody to herpes simplex. After her engagement to a man who was subject to cold sores she showed an increasing titer of this antibody. For the most part the virus remains quiescent, only bursting into activity through appropriate stimuli. These stimuli may be the result of irritation such as occurs from exposure to wind or sunburn in certain persons or in the presence of an infection such as a common cold. The cold sores are most numerous in the course of severe febrile infections such as malaria, meningococcus meningitis and pneumonias. Thus the virus is brought into activity by a large number of excitant causes including some virus diseases. This example of a latent virus infection brought into renewed activity by extraneous and internal excitants is of significance in the interpretation of many phenomena in the virus field.

Relation of Herpes Zoster and Chickenpox.—In 1893 von Bokai²³ of Budapest advanced the idea that chickenpox and herpes zoster (shingles) were different expressions of the same disease. He cited numerous examples of one following exposure to the other and offered the information that the autumn rise in the incidence of chickenpox was preceded by a rise in the incidence of shingles. The literature abounds in accounts to support this view. Laboratory workers then offered serological support for this idea, so that an etiologic relationship between these two diseases has become rather generally accepted in spite of the fact that neither of these diseases offers clinical immunity to the other.

It is well to recall that chickenpox was at first thought to be a modified form of smallpox, and that this conception was championed by

celebrated teachers in Vienna, Paris and Edinburgh Sahli in 1925 was the last. Here again it was recognized that these two diseases did not offer clinical immunity to each other. Throughout this long debate much the same sort of evidence was advanced as is now brought forward in support of the etiologic unity of chickenpox and herpes zoster.

Rivers and Eldridge²⁴ have thrown new light on this subject. They showed that in New York City the incidence of herpes zoster gives a straight line throughout the year, whereas the incidence of chickenpox rises in October and falls in June. Furthermore, intratesticular injections of chickenpox virus into monkeys developed tissue reactions with intranuclear inclusions. These reactions were prevented when convalescent chickenpox serum was added to the virus. On the other hand, if herpes zoster convalescent serum was added to the virus, the reaction took place. It is of interest that Goodpasture and Anderson²⁵ have been able to grow the virus of herpes zoster on a skin graft of the chick embryo, but not the chickenpox virus. Until further painstaking evidence from the laboratory comes to light it is well to bear in mind that these two diseases are clinically as far apart as chickenpox is from smallpox,* and herpes simplex from meningococcus meningitis. This last comparison carries the speculative implication that chickenpox and herpes zoster may activate one another. Much work is needed to support or contradict such a bold assumption.

German Measles (Rubella)—German measles has come into prominence as a result of the observations of Gregg²⁶ in Australia, confirmed by several observers in England and the United States. These indicate that this disease, when contracted early in pregnancy before the formation of the placenta, results in serious congenital defects in the fetus. These include congenital cataracts, congenital defects in the heart, and malformations of the mouth. In the second month of pregnancy miscarriage may occur, but if the fetus continues to term, over 90 per cent will show these serious defects. Prompt emptying of the uterus would allow pregnancy to be undertaken again under more auspicious circumstances. The relation of other virus diseases to early gestation has not as yet been sufficiently studied to warrant any conclusions. One thing to be learned from this is that no effort should ever be made to prevent girls from contracting German measles.

Poliomyelitis—Poliomyelitis is such a vast and familiar subject that we need to mention only a few pertinent facts. The virus is one of the smallest known. It is resistant to 1 per cent phenol, to 15 per cent ether, and to chlorination in the usual strength used to destroy enteric bacteria. It is killed by oxidizing agents such as hydrogen peroxide, potassium permanganate, by ultraviolet rays, and by heating to 55° C. for five minutes. It is normally a disease of man, and so far as is known

* Under certain conditions of the skin the character of chickenpox lesions can closely simulate mild smallpox, as well as herpes zoster.

is transmitted from man to man in the pattern of diseases of the upper respiratory tract. The portal of entry is the upper respiratory tract, and in the early acute stage it is spread from here. The virus is primarily neuronotropic, multiplying in the terminal neurons of the pharynx and the gastrointestinal tract. Thus the virus may be found in the stool. How much the stool plays in the spread of the disease is an open question, but recent studies strongly suggest its respiratory spread and show no evidence to support the idea that flies or other insects play an important part. Furthermore, a vast amount of epidemiological study tends to show that the disease is a common infection of man which in the majority of instances never reaches the central nervous system. When it does so we have clinical poliomyelitis. It has been shown that the virus may be present in the stool nineteen days before the onset of poliomyelitic symptoms. This with other clinical evidence suggests that it is unwise to extract tonsils when the disease is prevalent, because if the virus is present in the pharynx the trauma of the operation encourages extension of the virus to the medulla.

Once the virus gains access to the central nervous system we have a wide variety of clinical manifestations, depending on the severity of the inflammation set up and upon the portion of the central nervous system invaded. There may be only a mild encephalitis, as in mumps with no subsequent damage or we may have temporary or permanent damage to nerve cells. The recognition of what is going on is essential to effective treatment.

TREATMENT

We have no specific treatment against virus disease once the incubation period is passed. Convalescent serums supply antibodies, but after the virus is established in the cells and the incubation period is over it is questionable whether such serums are effective. That antiserums are effective early as a preventive is established. Convalescent measles serum and gamma globulin are particularly effective in preventing and modifying measles. Large doses of convalescent serum have apparently been effective in subduing various virus infections in the earliest stage,⁷ but these doses are not available to the practitioner.

In general the practitioner has no specific remedies with which to combat a virus once the incubation period is passed. The sulfa drugs and penicillin are of no avail.* Thus one is left to resort to symptomatic treatment. The mild infections of mumps, measles, German measles, chickenpox, herpes simplex and herpes zoster are self limited,

* Some of the exceptions to this are in that second group mentioned in the list of virus diseases where certain strains yield to penicillin or the sulfa drugs. Furthermore, moccasin venom in doses of 0.2 cc. subcutaneously is said to be effective in controlling herpes simplex on the cornea, and 2 per cent sodium iodide given intravenously in 20 cc. doses on alternate days for four doses is said to control herpes zoster of the cornea. (Personal communication from Dr. Paul M. Runge.)

and the natural recuperative powers do their work effectively if allowed to take their course

On the other hand, each of these diseases may present situations which call for prompt symptomatic treatment. Severe orchitis in mumps needs surgical interference to relieve pain. Encephalitis may be helped by lumbar drainage. Anoxemia requires oxygen administration. Dehydration must be combated with normal saline and glucose solutions. Catheterization and tidal drainage of the bladder may be necessary. Evacuation of the bowels is often a serious problem. Secondary bacterial infections must be treated promptly and adequately with sulfa drugs or penicillin. One of the undecided questions of today is whether an uncomplicated virus pneumonia should be given the benefit of penicillin as a routine preventive against secondary infections. In severe cases there is little doubt that such protective therapy is indicated.

In poliomyelitis one must distinguish between the bulbar and spinal forms of respiratory failure. The former must be combated with suction and postural drainage, the latter by the proper use of a respirator. The application of hot packs at appropriate intervals to relax muscle spasm and the avoidance of deformities are all essential to restoring the function of muscles. Furthermore, the weaning of patients from the respirator, the bringing back of muscles to usefulness through physical therapy, are of much more importance than the use of prostigmine and other drugs. There is no specific method or system of treating encephalitis or poliomyelitis. To imply that there is, is to ignore the fundamentals of medical practice, namely, that the physician should recognize what he is dealing with and attempt to overcome any and all obstacles to recovery by every possible means at his command.

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THE TREATMENT OF INFECTIOUS HEPATITIS (CATARRHAL JAUNDICE)

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DURING the recent war, the disease formerly known as "catarrhal jaundice" or "epidemic hepatitis" became exceedingly prevalent in many countries. Although service personnel was primarily affected, the number of civilian cases also increased strikingly. As a result, many studies on the nature of this disease have been feasible and have demonstrated two facts: (1) The disease appears to be infectious, its chief route of transmission probably being the ingestion of fecally contaminated material; (2) The pathological changes involve the liver as a whole and are not limited to the biliary duct system. In view of this newer knowledge, the disease is now called infectious hepatitis in this country. In England the term infective hepatitis is used. The actual infectious agent, however, has not been isolated, although it has many of the attributes of a virus.

Infectious hepatitis usually manifests prodromal symptoms such as general malaise, anorexia, aching, abdominal pain, chilly sensation, easy fatigability, nausea, vomiting, mental depression and other non-specific symptoms of general infection. Occasionally urticaria or arthralgia may be present. Later jaundice, hepatomegaly and splenomegaly of varying degrees may appear, but it is now well recognized that some patients may exhibit only the prodromal symptoms and never develop jaundice. Such patients are usually considered to have "intestinal gripe," "stomach flu" or the like, but liver function studies or examination of hepatic tissue reveals definite hepatic damage.

The incubation period of infectious hepatitis varies between two and four weeks. The severity of the prodromal symptoms and of the jaundice varies considerably. In mild cases subjective symptoms usually disappear soon after jaundice becomes apparent. In severe cases malaise, prostration, anorexia, nausea and vomiting may continue for some time after icterus is manifest. Sometimes stupor, ascites, edema and hemorrhagic phenomena may appear, and the disease may run the course of acute yellow atrophy. The mortality in sporadic cases

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is, however, very low and even in epidemics it is usually less than 1 per cent

Closely allied to infectious hepatitis is the so-called "homologous serum" or "syringe-transmitted" jaundice. This disease has a similar clinical, biochemical and pathological course, but its incubation period varies from two to four months, and it is transmitted by the infection rather than by the ingestion of infective materials. Any injectable substance may be infective if it contains or is contaminated with the blood, plasma or serum of a person who has, or recently has had "homologous serum" jaundice. In the case of contamination, the amounts needed to transmit the disease can be very minute—an improperly sterilized needle, for example, may be responsible.

The exact relationship between infectious hepatitis and "homologous serum" jaundice is not clear but the treatment of the conditions is similar. Unless otherwise indicated the therapeutic suggestions outlined below are intended to apply to hepatitis of either the infectious or "homologous serum" type.

TREATMENT

Bed Rest.—Bed rest is essential, for the patient is not only more comfortable, but the course of his disease as indicated by biochemical tests, duration of jaundice, and persistence of hepatic tenderness is beneficially affected.^{1 2 3 4} Even in the convalescence stage of the disease increased exercise can have a deleterious effect and may in some instances, lead to relapses.

CASE REPORT—A 30 year old physician, otherwise in good health suddenly experienced severe fatigue and diffuse arthralgia late in August, 1945. For several days thereafter he had malaise, chilly sensations, mild fever and severe anorexia. The most striking symptom was a complete "lack of pep." His only desire was to lie quietly in bed without doing anything. Even reading seemed to require extraordinary effort.

Five days after onset of his symptoms, he noted that his urine was darker than usual, and tests showed the presence of bilirubin. The next day hepatic tenderness and jaundice developed, and the liver was palpable. For one week malaise and anorexia continued, while the jaundice deepened until the bilirubin concentration in serum reached 8 mg per 100 cc. At this point many of his symptoms began to subside, but extreme lassitude and hepatic tenderness persisted.

The jaundice slowly subsided over a period of six weeks. At the end of this time the patient who had been on strict bed rest started to become ambulatory. Almost immediately soreness in the hepatic area and tenderness to examination, both of which symptoms had been absent for two weeks while the patient was in bed, reappeared with rather pronounced intensity. There was no rise in the serum bilirubin at this time. Subsequently whenever the patient exerted himself unduly the same hepatic soreness and tenderness recurred. This symptom thus provided a good measuring stick with which the patient's return to activity could be controlled. With very gradual increases in the amount of his physical exertion the patient finally was able to resume full activity but a period of two months elapsed between the disappearance of the jaundice and the complete subsidence of all pain in the hepatic area.

As this case suggests, the duration of necessary bed rest is variable and must be evaluated on the symptomatology and progress of each case. On the average, the liver of jaundiced patients remains tender and enlarged for a period of two weeks, consequently, complete bed rest for a minimum of three weeks should be instituted for all cases. Bed rest beyond this period is indicated by the following signs and symptoms

- 1 A sore, tender or enlarged liver, particularly after physical exertion
- 2 Hemorrhagic phenomena
- 3 Clinical icterus or bile in the urine. The icteric index should be less than 15 and the serum bilirubin level less than 1.5 mg per 100 cc before the patient is mobilized
- 4 Nausea, vomiting, anorexia, drowsiness, lack of interest. Easy fatigability often persists into the convalescent stage and does not by itself require further bed rest
- 5 Impaired hepatic function as indicated by hepatic function tests. In some patients, mild impairment of bromsulfalein excretion, which may persist for months, can be ignored if the patient is well by all *clinical* standards

After the patient is mobilized, increased activity should take place very gradually. On the average, at least three weeks should elapse between getting the patient out of bed and allowing him to return to work.

Diet.—Low fat diets, containing abundant proteins, carbohydrates and factors of the vitamin B complex, protect healthy laboratory animals from severe liver damage when the animals are exposed to hepatic toxins^{5, 6}. A similar diet appears to benefit patients with chronic cirrhosis of the liver⁷. On the other hand, diets deficient in protein and vitamin B complex induce necrotic and cirrhotic changes in the livers of laboratory animals^{8, 9, 10}. These facts do not prove that the low fat, high protein, high carbohydrate diet, reinforced by vitamin B complex, is the diet of choice in the treatment of infectious hepatitis, but the evidence is strongly suggestive, and the type of diet given in Table 1 is usually recommended. On the other hand, recent clinical studies suggest that diets containing as much as 100 gm of fat per day are not injurious and may even help the patient to gain weight. The fat content of the diet and feeding given in Tables 1 and 3 can easily be increased by using whole instead of skim milk. The chief difficulty in using a diet containing abundant fat is that the protein and vitamin B complex intake may be reduced as the patient receives calories from other sources.

Whatever the diet, it is important that the patient eat something, a feat which may be difficult to accomplish in face of the severe anorexia, nausea or vomiting which often attend infectious hepatitis. Food must therefore be palatable and attractively prepared. If a patient cannot eat, tube feedings or parenteral alimentation should be under-

TABLE 1—DIET FOR INFECTIOUS HEPATITIS

Total Calories 2500 to 4000 per 24 hours

Division of Calories

Carbohydrate	65 to 75 per cent
Protein	20 to 25 per cent
Fat	5 to 10 per cent

General Rules

- 1 All fat and fatty foods are to be avoided except for 1 pat of butter which is allowed with each meal. This allowance gives the patient 25 gm. of fat in the form of butter per day but it is not harmful provided the protein and vitamin B complex intakes are adequate. In fact butter by making the diet more palatable, may actually increase the amount of protein and carbohydrate ingested.
- 2 Alcohol in any form must be avoided completely.
- 3 The daily protein intake should be 150 gm. or higher. This intake can be achieved if the patient takes the following amounts of protein rich foods every day:

Skim milk	1½ quarts
Dried skim milk powder given beaten up in soups, milk desserts, mashed potato etc. (Large milk companies can often supply dried skim milk powder. If not, the local bakery usually knows where it may be obtained.)	3 ounces
Lean meat, chicken or fish (see diet lists below)	¼ to ½ pound
Cottage cheese	¾ cup
Egg white	2
Dried brewers yeast	6 heaping teaspoons
- 4 A high carbohydrate intake should be achieved by giving the patient sweetened fruit juices by using as much sugar, honey and sweet syrups as possible and by offering hard sugar candies after meals.
- 5 Dried brewers yeast (2 heaping teaspoons) is given in skim milk or fruit juice about 1 or 2 hours after meals. If given before a meal, it may depress the appetite. A late evening feeding may be offered if the calorie intake is maintained with difficulty.
- 6 The diet should be given for a period of 3 months. After this time if the patient has no residual evidence of liver damage whole milk and whole egg may gradually be used instead of skim milk and egg white. After 6 months, the patient may be allowed to return to an unrestricted diet. The brewers yeast supplement can also be omitted between 3 and 6 months after the onset of the hepatitis. Alcohol should be avoided for at least 6 months.

Food to Use

Fruits and fruit juices Sweeten as tolerated. Glucose (dextrose) is not as sweet as cane sugar; hence more carbohydrate can be given if glucose is used for sweetening.

Cereals All types cooked or uncooked.

Bread Wheat or rye as desired.

Sugar jelly jam honey maple syrup molasses As desired.

Eggs Whites as desired. Egg white may be used in cooking, desserts, fruit whips. One yolk may be used daily in place of 1 pat of butter.

TABLE 1 —DIET FOR INFECTIOUS HEPATITIS—*Continued*

Beverages	Skim milk, dried skim milk, ginger ale, fruit drinks, black coffee, clear tea	The chief disadvantage of coffee and tea is that they fill the stomach without supplying calories	Coffee, vanilla or a <i>small amount</i> of cocoa may be used as flavoring
Soups	Vegetable soups, vegetable cream soups made with skim milk, bouillon, consommé		
Meat	Lean beef, lean lamb, lean chicken, calf liver, lean veal	Serve roasted, boiled or broiled	No gravies or sautés Use lean meat or fish twice daily if possible
Fish and shellfish	Sole, flounder, haddock, halibut, cod, lobster, shrimp	Do not prepare or serve with any fatty material except with daily butter allowance	
Cheese	Cottage cheese	Serve with lettuce and fruit, or baked with macaroni	
Starches	Potatoes (mashed, baked, boiled), rice, macaroni, noodles (not egg), spaghetti as desired	Do not use fatty sauces	A "cream sauce" can be prepared by mixing skim milk and flour in a shaker and cooking in a double boiler
Vegetables	Asparagus, carrots, peas, beets, spinach, lima beans, squash, string beans, broccoli, tomatoes, lettuce		
Desserts	Fruits (chiefly cooked or canned), gelatin desserts, cornstarch and rice puddings, fruit sherbets, junket (skim milk), baked banana, tapioca, angel cake, candy made of egg white and sugar		

Foods to Avoid

Unless foods are specifically mentioned on the diet list, they should not be used The patient, however, should be cautioned against

All fried foods

Salad dressings

Chocolate

Nuts

Vegetables, desserts or any other food prepared with butter, cream or other fats

Crackers and cookies Some have a fairly high fat content

taken, but how much nourishment a badly damaged liver can handle is an unsettled question Judging from the results of liver function tests, it appears unlikely that such livers can metabolize their usual quota of carbohydrates and proteins On the other hand, starvation may intensify the noxious processes taking place in the liver or may prevent regeneration of normal liver cells Some nourishment must consequently be made available to the patient, the exact amount depending on the degree and duration of the impaired food intake

For patients who must be tided over a brief but acute phase of anorexia and vomiting, intravenous nourishment is indicated This procedure not only provides food, but often brings about marked symptomatic improvement.

The mixture given in Table 2 provides 1000 calories daily A 15 per cent solution of glucose supplies more calories but may cause venous thromboses The other alternative—giving more of the 10 per cent solution—may prove difficult for no more than 500 cc of this solution

should be administered per hour¹² If the patient is losing salt and water because of vomiting, diarrhea or high temperature, the fluid and salt intake should be increased.

Protein material and more calories can be supplied by adding 20 gm. of a parenteral amino acid preparation to each 1000 cc. of 10 per cent glucose solution. Under ordinary conditions a considerable

TABLE 2—PARENTERAL FEEDING PER 24 HOURS

10 per cent glucose in 0.85 per cent NaCl solution	500 cc
10 per cent glucose in water	2,000 cc
Ascorbic acid	200 mg
Nicotinamide	50-100 mg
Thiamine	10 mg
Riboflavin	10 mg

Note Many parenteral preparations containing several factors of the vitamin B complex include pantothenic acid and pyridoxine.¹¹ The human requirements for these vitamins have not been established. In the near future preparations containing "folic acid" will probably become available.

amount of amino acids so given may be consumed for energy purposes if the glucose given simultaneously is not adequate to cover these needs. What happens when hepatic function is grossly deranged is not definitely known. The addition of amino acids to a 10 per cent solution of glucose unfortunately increases the likelihood of a thrombophlebitis at the site of injection. Nevertheless amino acids are indicated if the

TABLE 3—SIMPLIFIED MIXTURE FOR TUBE FEEDING (24 HOUR AMOUNT)

Skim milk	2 quarts
Dried skim milk powder	6 ounces
Brewer's yeast powder	1 ounce
White of two eggs	
Corn syrup (Karo etc.)	4 ounces
Ascorbic acid (grind up tablet)	100 mg
Fish liver oil concentrate	Vitamin A 5000 units
	Vitamin D 1000 units

Directions Beat up white of eggs and add corn syrup. Make paste by adding small amount of skim milk to dried skim milk powder and brewer's yeast powder. Beaten egg white and paste can then be stirred into the remaining amount of skim milk.

major part of a patient's nourishment has to be given by parenteral routes for more than two days.

In patients suffering from prolonged anorexia without too much vomiting, tube feedings are used with advantage (Table 3). The simplified mixture provides 2000 calories and 150 gm of protein per day. It can be divided into three equal parts and administered at 8 A.M.

2 P.M., and 8 P.M. Since it is fluid and nonviscous, the mixture can be allowed to drip slowly into the stomach by gravity, one hour being allowed for each feeding. Usually the tube should be inserted for each feeding and then withdrawn.

Additional calories can be given if desired by adding more sugar or corn syrup to the tube-feeding mixture. Very hypertonic solutions, however, greatly delay gastric emptying and may aggravate any tendency the patient has to vomit. More skim milk powder may also be added if additional proteins are desired.

Medications—Vitamins—The diet should be fortified by a liberal supply of crude *vitamin B complex*. Preferably 2 to 3 heaping teaspoonfuls of granulated or powdered brewers' yeast are given three times daily about one to two hours after meals. Such therapy provides all the factors of the vitamin B complex as well as additional proteins (the protein content of dried brewers' yeast is almost 50 per cent). In order to make the yeast palatable, it should be beaten up in skim milk or tomato juice. Some patients, however, may not be able to take large amounts of yeast in any form. In this case, 4 tablets (or capsules) of concentrated vitamin B complex should be given three times daily.

Vitamin C is adequately supplied by the fruit of the diet (Table 1).

Although plasma *vitamin A* levels are depressed in hepatitis, there is no evidence that the body's stores of this vitamin are depleted. Since the patient is on a low-fat diet, however, a fish liver oil concentrate containing about 5000 units of vitamin A and 1000 units of vitamin D should be given daily.

Vitamin K—In patients with severe or prolonged hepatitis, a bleeding tendency produced by a decreased blood prothrombin content may become apparent. This disorder of the clotting mechanism in hepatitis is more often caused by an impaired utilization of vitamin K by the liver than by an impaired absorption of the vitamin. Nevertheless, all hepatitis patients exhibiting a prolonged prothrombin time, a bleeding tendency, or an icterus index over 75 should receive about 4 mg. of a water-soluble parenteral vitamin K preparation (Synkayvite, Hykinone, Synkamin) every two days.¹¹

Lipotropic Factors—Among the liver-protecting substances present in crude vitamin B complex and in protein, the most important appear to be *choline* and the sulfur-containing amino acids, *methionine* and *cystine*.^{8, 9, 10, 13} Methionine and choline are "lipotropic," i.e., they mobilize or prevent deposition of abnormal excess fat depots in the liver. Their lipotropic properties depend on the fact that both substances have methyl groups which appear necessary for hepatic fat metabolism, presumably for the conversion of neutral fats to phospholipids.¹⁴ This point is of practical importance, for cystine, which does not contain any methyl groups, may actually harm the liver in experimental animals.

unless methyl groups from some source, such as choline, are given simultaneously⁹

Certain facts—frequently ignored—must be emphasized

1 Methionine protects the liver of a protein depleted animal if it is given *before*, or within four hours after, the liver is exposed to a toxin. It exerts no beneficial effect if given more than four hours after the animal is subjected to the hepatotoxic agent.¹⁵

2 Methionine and choline protect the liver of a protein-deficient animal. There is no evidence that the animal which has been on a well balanced diet is benefited by "extra" methionine and choline

3 Little is known concerning the effects and actions of choline or methionine on a liver damaged by infectious hepatitis

In view of these facts the theoretical efficacy of choline and methionine in the treatment of infectious hepatitis may be questioned, especially if these substances are used after the appearance of jaundice. If given in the prodromal period they may have some effect, but punch biopsies show that the liver parenchyma exhibits definite pathologic changes well before the onset of jaundice.¹⁶ From the clinical viewpoint, methionine has been said to benefit toxic hepatitis^{17 18} and choline with cystine has apparently induced improvement in patients with severe cirrhosis.⁷ On the other hand, the treatment of infectious hepatitis with these lipotropic substances has led to equivocal results.¹⁹⁻²³ It would seem reasonable to conclude, on the basis of present knowledge, that the use of choline, cystine and methionine should be restricted to the very early cases or the very sick patients

Choline chloride, cystine and methionine can be given orally or intravenously but the optimum daily doses have not been established. For methionine, the daily administration of 5 to 12 gm. has been advocated.^{18 19} The usual dose of choline and cystine has ranged between 2 and 10 gm. of each per day.^{7 24} If the sulfur-containing amino acids are given intravenously, a 2 per cent solution in normal saline solution may be used, but the infusion should be given slowly over a period of at least three hours. In the case of choline, intravenous administration must be undertaken with caution, since excessive secretions, bronchial spasm, abdominal cramps, flushing and perspiration may occur and may have to be treated with atropine sulfate grain 1/100 subcutaneously every four hours as needed.²⁵

Unfortunately, the lipotropic factors are not readily available at present. Methionine* is expensive and difficult to obtain, whereas choline, an extremely deliquescent substance, is not marketed in a convenient form for dispensation. The high protein diet fortified with dried brewers yeast, however, provides a not inconsiderable amount of the lipotropic agents. The tube feeding (Table 3), for example, furnishes about 4 gm. of methionine per day (Skim milk contains approximately

* A preparation of methionine called Neomine (Weth) may soon be available.

0.1 per cent, and dried skim milk 1 per cent methionine) The vitamin B complex, furthermore, provides other lipotropic factors, such as inositol

Antipruritics—Itching does not occur too commonly with infectious hepatitis. When it does, local application of calamine lotion containing 1 per cent phenol affords definite if not complete relief. Intravenous calcium gluconate (10 cc of a 10 per cent solution) or procaine (1 gm in 1000 cc, given over two hours) often help considerably, but the effect is transient^{26, 27}

Sedatives—Morphine or any opium derivatives should never be used in the treatment of hepatitis. Barbiturates are also best avoided, if they are employed, the dose should be one third or at most one half the usual dose. Chloral hydrate and paraldehyde probably have little deleterious effect on the liver, but their taste may increase nausea and vomiting. For severe cases of restlessness and confusion, paraldehyde may be used parenterally.

PREVENTION

Precautionary Measures.—Since infectious hepatitis is spread principally through fecal contamination, the stools of all patients with this disease should be handled with extreme care. Probably the safest procedure is to take the same precautions with the stool as in a typhoid case. In addition, eating and washing utensils should be sterilized in boiling water, visitors should not be allowed to come into direct contact with the case, and those taking care of the patient should observe scrupulous care in washing their hands. Unfortunately, as is true of many virus diseases, the most infective period is the early prodromal phase when the absence of icterus makes diagnosis difficult.²⁸

The prevention of "homologous serum" jaundice depends on two major precautions:

1. Do not use blood or blood products from anyone who has had jaundice or a severe, unexplained "grippe" within one year.

2. Sterilize all syringes and needles carefully. It has been recommended²⁹ that all syringes and apparatus used for intravenous or intramuscular injection be sterilized by dry heat (160°C for one hour). If this is impossible, the apparatus should be carefully cleaned and placed in boiling water for twenty minutes after each use. Even when blood is drawn for laboratory purposes, a clean and sterilized needle and syringe are used with advantage. For chemical disinfection, "the only permissible disinfectant is 70 to 75 per cent alcohol," in which disassembled syringes must be placed for five minutes.²⁹

Gamma Globulins.—The "gamma" fraction of human plasma globulins contains a high titer of antibodies for various diseases and is available in several states for the prevention or attenuation of measles. Gamma globulins are also of benefit in the prevention or attenuation

of infectious hepatitis provided they are administered intramuscularly during the incubation period. The dose which has been used is 10 cc. for adults and 0.075 cc per pound for children^{30 31}. Once the prodromal, pre icteric phase of the disease has begun, gamma globulins are ineffective³². Their use is therefore restricted to the prevention of infectious hepatitis in institutions, camps and military units after the members of such groups have been exposed to a known case. "Homologous serum" jaundice apparently cannot be prevented by the administration of gamma globulins in the incubation period.³³

SUMMARY

Infectious hepatitis (catarrhal jaundice) is an infectious disease frequently transmitted by fecal contamination. Its treatment consists of absolute bed rest for a minimum of three weeks, a low fat high protein, high carbohydrate diet, and 1 ounce (30 gm) of dried brewers yeast daily. Other vitamins and lipotropic factors may be indicated in certain cases. The spread of the disease should be controlled by careful disposal of the feces and sterilization of the patient's utensils, bedclothes and the like. In institutions, infectious hepatitis may be prevented or attenuated by the use of gamma globulins during the period of incubation.

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THE EMERGENCY TREATMENT OF MYASTHENIA GRAVIS

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MYASTHENIA GRAVIS, a somewhat rare and often fatal disease prior to 1935 when treatment by neostigmine (prosthigmine) was instituted, has become in the last decade a disease more commonly reported. The fatality rate up to ten years ago was high about half of the patients dying in the hospital during the period of initial observation and another 25 per cent dying within a year or two after the diagnosis was made. In the last ten years in our Clinic, about 170 cases have been observed. During this period, thirty five patients have died, a considerable number of them being in the older age groups where death was not unexpected. Most patients die a respiratory death either due to the fatigability of the muscles of respiration or to aspiration of food into the respiratory tract where dysphagia is a marked symptom of the disease. Some of these deaths could have been avoided if prompt and energetic treatment had been used. Treatment depends necessarily on diagnosis and until the disease is fully recognized no form of treatment can be instituted which is likely to be effective.

DIAGNOSTIC CRITERIA

Myasthenia gravis can be recognized at the present time by simple means. No other disease has as its outstanding characteristic excessive fatigability of the voluntary muscles with recovery taking place as the result of rest or of medication. The disease, moreover almost never runs a progressive downhill course, so commonly observed in degenerative conditions of the nervous system with muscular weakness but progresses by natural or spontaneous remissions and relapses. This course is so characteristic of myasthenia gravis that it becomes an essential part of the diagnosis.

At the beginning of the disease, however before enough time has elapsed so that the course of the disease can be adequately evaluated diagnosis depends upon the signs of response to rest or to medication. Patients will usually indicate to the observer, if the muscles have shown considerable weakness that without an adequate period of rest normal use of the muscles is not possible. In addition to rest, improvement may be demonstrated under neostigmine, the response usually being so marked in this disease and slight in all other diseases that the drug is of diagnostic as well as therapeutic value. Neostigmine methylsulfate

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(15 mg) is combined with atropine sulfate (0.6 mg) in a single ampule for the diagnostic test. A scheme has been elaborated to evaluate the results.¹

EMERGENCY TREATMENT

Patients with myasthenia gravis are ordinarily treated with neostigmine bromide (15 mg) tablets taken by mouth in appropriate doses at intervals during the twenty-four hours. This usually suffices to maintain most patients in reasonably good health. As some patients, however, may have respiratory crises or difficulty in swallowing, all patients should be familiar with the parenteral use of the drug in the form of the neostigmine methylsulfate. Thus, patients who are ambulatory and ordinarily without severe symptoms should always be in a position to obtain an injection promptly when the need arises. In our Clinic, patients are furnished with ampules of neostigmine methylsulfate (0.5 mg). When severe symptoms develop, two ampules should be given to an adult, either subcutaneously or intramuscularly. A hypodermic needle may be used. Any qualified person can give the drug to the patient. The patient or a member of his family may be taught to give an injection exactly as in the treatment of diabetes or other diseases where a deficiency exists. In myasthenia gravis, indeed, neostigmine should be considered as a deficiency drug. In most instances an even maintenance of the drug can be provided by oral medication throughout the twenty-four hour period. It is for the emergency, however, that the drug is usually given in the soluble form. A dose of 1 mg may be given up to two or three times within a period of an hour if good results are not obtained from the initial injection. Usually, patients respond promptly and a second injection is seldom needed.

In order that the patient may receive prompt attention even if a physician is not readily available, each patient in our Clinic is given a form letter, as follows:

TO PHYSICIANS OR NURSES CALLED UPON TO TREAT PATIENTS WITH MYASTHENIA GRAVIS

John Doe, Unit No. 000000, a patient attending the Myasthenia Gravis Clinic of the Massachusetts General Hospital, is taking an adequate amount of neostigmine (prosthigmine) bromide (15 mg) tablets by mouth in order to care for ordinary symptoms. The patient, however, occasionally has difficulty in swallowing and breathing. Under such circumstances, the oral medication should be reinforced by intramuscular injections of neostigmine methylsulfate (ampules 0.5 mg). In order to be prepared for such a contingency, the patient has been supplied with ampules for deep hypodermic injection. In case of emergency, the medicine therefore is available and if given promptly may overcome an attack of respiratory embarrassment or marked difficulty in swallowing. Two ampules should be given at one time. This dose may be repeated in one-half hour if improvement has not taken place.

This communication is to be used only by the patient or patient's family in case of emergency, and is designed to aid the family physician or a nurse in giving

the proper amount of medicine promptly. As the disease is not common, it is quite possible that the patient's attendant may not be familiar with the above procedure.

If there is occasion for any physician to write to the hospital about this patient, please refer to the above unit number and address the letter to the Social Service Department, Myasthenia Gravis Clinic, Massachusetts General Hospital, Boston 14, Massachusetts. In case of emergency the neurological resident at the hospital may always be called by telephone.

CASE HISTORIES

The use of neostigmine is illustrated by selected case histories. The first discloses the method of establishing the diagnosis and bringing the patient to a point where treatment can be given and the patient well maintained. The emergency here is not a matter of life and death but is associated with a competent diagnosis and an evaluation of the effect of the treatment in preventing continued marked involution.

CASE I (Mrs. D. A. W., U360999) — *Insidious onset at age 27. General weakness with remissions during two pregnancies; positive neostigmine test; treatment omitted and patient bedridden for six years; full recovery after treatment given; maintained for at least four years.*

neostigmine bromide by mouth and resumed her normal activities, walking up and down stairs without difficulty, going shopping and being fully maintained on an intake of 6 to 9 tablets a day²

When last seen in March, 1946, four years after the initiation of an adequate maintenance schedule of neostigmine bromide by mouth at appropriate intervals, the patient was almost symptom-free and able to carry out all the ordinary activities of a housewife

Comment—This case history illustrates the value of correct diagnosis and prompt establishment of treatment. This patient, long an invalid and indeed once confined to bed, was able to resume her normal activity when properly cared for. The fault arose here in the action on the



Fig 136—The "myasthenic facies"

part of someone in allowing the patient to remain in a state of invalidism. The use of oral neostigmine resulted in the release of muscle power that, for some unknown reason, was held in abeyance by a factor of the disease not recognized at the present time. The patient's muscles were in a state that resembled one of partial curarization, in which continuous and excessive fatigability was a prominent feature. That the body may control this unknown factor is shown by the spontaneous remissions characteristic of the disease and by complete freedom of symptoms that may occur during the last six months of pregnancy.

The rapid onset of symptoms, particularly in the old age group, call for prompt diagnosis and treatment. Patients with dysphagia lose

weight rapidly and become quickly debilitated. Time may be lost by a consideration of bulbar palsy or cancer of the esophagus as possible causes of dysphagia. An examination of the swallowing reflex with barium under the fluoroscope, often serves to make the diagnosis unquestionable.

CASE II (B. C., U 419365)—*Rapid onset of dysphagia at age 60 nasal regurgitation of fluids loss of 30 pounds in weight positive neostigmine swallowing test, adjusted on oral medication with supplemental injections complete remission in seven months no symptoms in last two years*

At the age of 60 in 1943, the patient suddenly developed transient ptosis of the lids soon followed by dysphagia. There was increasing difficulty in getting food into the pharynx. Liquids regurgitated through his nose. His voice became nasal in type and secretions collected in his nasopharynx, with coughing and gagging. Bulbar palsy and cancer of the esophagus were considered as probable diagnoses. The dysphagia was promptly relieved by a diagnostic ampule of neostigmine and the swallowing reflexes studied with barium under fluoroscopy became normal within twenty minutes of the injection.² A diagnosis of myasthenia gravis was made after observing that the barium no longer was retained in the pharynx, pyriform sinuses or valleculae (Figs 137 and 138). The patient was quickly adjusted to 12 tablets of neostigmine bromide by mouth given every two hours from 8 A.M. to 10 P.M., plus two injections of neostigmine methylsulfate (0.5 mg.) at 12 noon and 6 P.M., before the principal meals of the day.⁴ Thirty five pounds in weight was gained in a few weeks under this treatment. A remission started almost at once and seven months later the patient was completely free from symptoms without the need for any medication. He has remained well for the last two years during which time he has had an operation for varicose ulcers, without recurrence of symptoms of myasthenia gravis.

Comment—This case illustrates the rapid onset of the disease, as well as the possibility that the first symptoms may occur in a patient of 60 years of age. Of 125 patients in our early series twenty-one had their first symptoms between ages 60 and 70 and five between ages 70 and 80. In fifty-four of the 125 cases the disease first appeared at 40 years of age or over. It thus is not uncommon in persons past 40 a fact not fully recognized in most clinics. Some cases, moreover have a rapid onset, usually of two or three weeks duration. The importance of prompt diagnosis in this group cannot be overemphasized, since death has been known to occur in a few weeks. Indeed, this was not uncommon before the days of neostigmine treatment. In cases in which dysphagia is the presenting symptom, the diagnosis can readily be made by the neostigmine test.

This case also makes clear the value of supplemental treatment by injection chiefly before the main meal of the day so that a patient may not lose weight when suffering from dysphagia.

Finally if a patient is carried through a relapse, no matter how severe, the possibility of a remission, either partial or total, must always be kept in mind.⁵ In this case the remission was complete and has lasted two years. We must remain aware however that a relapse may



Fig 137 —Retention of barium in the hypopharynx, pyriform sinuses and valleculae.



Fig 138 —The normal swallowing reflex, twenty minutes after injection of 1.5 mg of neostigmine methylsulfate and 0.6 mg of atropine sulfate, intramuscularly

occur in the future, although remissions have been known to last as long as twenty years

THE DIAGNOSIS AND TREATMENT OF ANEMIA

BERTHA L. PAEGEL, M D * AND JOSEPH F. ROSS, M D †

ANEMIA is one of the most common abnormalities afflicting the human race. Between 12 and 25 per cent of all patients admitted to large general hospitals in the United States have been shown to have definite anemia,^{1, 2} and more than half of all school children and women in certain economic classes in both England and the United States have abnormally low levels of hemoglobin.^{3, 4, 5} It is highly probable that the incidence of anemia is even higher in other regions of the world in which poorer standards of living prevail. It is impossible to estimate the loss of physical efficiency and general disability attributable to this widespread anemia, but it is undoubtedly extremely great. A decrease in the hemoglobin level of only 10 or 15 per cent is frequently sufficient to produce definite asthenia and easy fatigability in otherwise perfectly normal individuals.

Fortunately, the vast majority of patients with anemia respond very readily to proper therapy, and can be completely cured by relatively simple and inexpensive therapeutic measures. Indeed, the very simplicity and inexpensiveness of these measures apparently mitigate against their proper and widespread application. It is interesting in regard to the economics of drug production and the effectiveness of advertising measures to consider the multimillion dollar vitamin industry, which sells the public vast quantities of unneeded vitamins, while the inexpensive and readily accessible element, iron, still constitutes one of the major dietary deficiencies of the world.

There are few diseases in which so exact a diagnosis can be established by clinical and laboratory studies as in the various anemias. Furthermore, the measures required to establish definitely the type of anemia are easily performed and quite inexpensive. In spite of these facts, however, it is safe to say that few pathological conditions are treated more ill-advisedly. It is seldom, indeed, that a patient with simple iron-deficiency anemia is not treated with large amounts of vitamins and various types of parenteral liver extract, substances which repeatedly have been demonstrated to be completely ineffective in relieving this type of disease.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine. Prepared under tenure of a Welch Fellowship in Internal Medicine.

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Rational and effective treatment of anemia depends upon the determination of the exact nature and etiology of the condition. Therapeutic measures which will be strikingly effective in one type of anemia may be entirely useless in a different type. Attempts to combine all therapeutic measures into a single "shotgun" remedy, which can be given indiscriminately to every patient with anemia, not only result in an unnecessary expense to the patient, but also may fail to produce adequate blood regeneration. Moreover, "shotgun" nonspecific therapy may obscure a serious underlying disease of which the anemia is only a superficial sign. It is not only advantageous from an academic standpoint to establish the exact cause of any case of anemia, but it is also economically and practically sound to do so.

In general, the commonly encountered types of anemia can be grouped into three main classes: (1) anemias due to an inadequate supply of substances essential for erythrocyte and hemoglobin formation, (2) anemias due to defective functioning of the bone marrow, and (3) anemias due to too rapid loss or to a rapid destruction of erythrocytes. Each of these main types of anemia has characteristic clinical features, and the characteristics of the peripheral blood and of the bone marrow are quite distinctive. The successful therapy of each type is also quite specific.

DIAGNOSIS OF ANEMIA

The existence of the anemic state usually can be readily diagnosed from the careful inspection of the color of the conjunctivae, the mucous

TABLE 1 —DIAGNOSTIC TESTS IN ANEMIA. NORMAL VALUES

Hematologic Determination	Normal Values	
	Male	Female
Hemoglobin (grams per 100 cc. blood)	14.5-18.0 gm %	12.0-15.0 gm. %
Hematocrit (per cent)	43-49%	38-43%
Erythrocyte Count (per cu. mm. blood)	4,800,000-5,800,000	4,000,000-5,000,000
Reticulocyte Count (per cent of total erythrocytes)	0.5-1.5%	0.5-1.5%
Icteric Index (units)	4-7	4-7

membranes and the skin of the patient. In some instances the coexistence of other physical features gives material aid in establishing the type of anemia. Thus in pernicious anemia the classical findings of gray hair appearing at an early age, a smooth, red, and frequently sore tongue, a faint icteric tinge to sclerae and skin, curved fingernails, and

TABLE 2 --CELL INDICES SIGNIFICANCE, METHODS OF CALCULATION AND NORMAL VALUES

Cell Indices	Significance	Method of Calculation	Normal Values
Mean Corpuscular Volume ("MCV")	Average volume of the erythrocytes	$\frac{\text{Hematocrit in } \% \times 10}{\text{Erythrocyte count in millions/cu mm}}$	80-95 cubic micra
Mean Corpuscular Hemoglobin ("MCH")	Average <i>weight</i> of hemoglobin per erythrocyte	$\frac{\text{Hemoglobin in gm } \% \times 10}{\text{Erythrocyte count in millions/cu mm}}$	30-34 micromicrograms
Mean Corpuscular Hemoglobin Concentration ("MCHC")	Average <i>concentration</i> of hemoglobin per erythrocyte	$\frac{\text{Hemoglobin in gm } \%}{\text{Hematocrit in } \%} \times 100$	31-34%

signs of involvement of the dorsal and lateral columns of the spinal cord usually serve to establish the diagnosis. In various types of hemolytic anemia the occurrence of definite icterus, unassociated with bile in the urine, the presence of a markedly enlarged spleen, and the occasional occurrence of congenital or familial physical abnormalities may prove helpful. By far the great majority of anemic individuals, how-

TABLE 3—CELL INDICES VALUES IN VARIOUS TYPES OF ANEMIA

Type of Anemia	Cell Indices		
	MCV cu micra	MCH micromicrograms	MCHC %
Microcytic hypochromic	Under 80	Under 30	Under 31
Normocytic normochromic	80-95	30-34	31-34
Microcytic normochromic	Under 80	Under 30	31-34
Macrocytic "hyperchromic"	Over 95	Over 34	34 or less

TABLE 4—CLASSIFICATION OF ANEMIAS ON THE BASIS OF CELL INDICES

Microcytic Hypochromic Anemias

Iron-deficiency anemia

Cooley's anemia

Normocytic Normochromic and Microcytic Normochromic Anemias

"Physiologic" anemia of pregnancy

Anemia following acute blood loss

Anemia due to "toxic depression" of bone marrow as in renal disease and chronic infection

"Aplastic anemia"

Myelophthistic anemia, as in metastatic carcinoma

Macrocytic Anemias

Pernicious anemia

Sprue and sprue-like states

Pernicious anemia of pregnancy

"Nutritional macrocytic anemia"

"Achromic anemia"

Anemia of *Diphyllobothrium latum* infestation

Macrocytic anemia of liver disease

Macrocytic anemia of hypothyroidism

Hemolytic anemias (occasionally macrocytic)

Myelophthistic anemias (occasionally macrocytic)

ever will fail to show any specific diagnostic physical abnormalities other than the previously noted pallor. Although the history may be helpful in indicating a site of chronic blood loss, a family history of anemia or a suggestive history of subacute degeneration of the spinal cord the actual establishment of the type of anemia must be made by

laboratory investigation Fortunately, a few simple, carefully performed laboratory procedures are sufficient in most instances Such studies do not require elaborate equipment or time-consuming technics, and they may be carried out in any physician's well-equipped laboratory These laboratory procedures are directed toward determining the following (1) the concentration of the erythrocytes and hemoglobin in the circulating blood, (2) the size or volume of the erythrocytes, (3) the concentration of hemoglobin in these erythrocytes, (4) the rate of blood formation, and (5) the rate of blood destruction The diagnostic procedures necessary for determining these facts are indicated in Table 1

Based on the above determinations, practically all anemias can be classified into four morphological groups (1) microcytic hypochromic, (2) normocytic normochromic, (3) microcytic normochromic or (4) macrocytic "hyperchromic" anemia When this morphological description of the anemia is combined with studies of the rate of blood formation (reticulocyte count) and the rate of blood destruction (serum bilirubin, or icteric index), most cases of anemia can be classified as to etiology and as to indicated therapy Classification of the anemias into these four morphological groups is greatly facilitated by calculation and use of the cell indices, which describe the average erythrocyte volume, hemoglobin content and hemoglobin concentration⁶ These indices and their significance are shown in Tables 2, 3 and 4.

THERAPY OF ANEMIA

MICROCYTIC HYPOCHROMIC ANEMIA

Anemia characterized by microcytic hypochromic erythrocytes is by far the most common form of anemia With the exception of Cooley's anemia, which will subsequently be discussed, this form of anemia is almost invariably due to deficiency in body iron This deficiency usually arises from an interaction of two factors first, an increased demand for iron for the formation of more hemoglobin, and secondly, a decreased and inadequate supply of iron Increased demand for iron usually arises from one of the following factors (1) blood loss, (2) growth and (3) pregnancy By far, the most important of these is chronic blood loss A decreased supply of iron arises either from a poor dietary intake or from the poor absorption of iron from the gastrointestinal tract, and probably most commonly from a combination of these two factors

One of the most important features in the treatment of an individual with iron-deficiency anemia is the determination of the exact reason why iron deficiency should have developed Always in adult men, and frequently in women, anemia is the first sign indicating hidden blood loss Often this blood loss may be from an otherwise asymptomatic neoplasm of the gastrointestinal tract Proper attention devoted to

tinal symptoms than do the ferric salts. Consequently, ferrous salts are preferred for therapeutic purposes. Of the various forms of ferrous salts available, simple ferrous sulfate is fully as effective and far less expensive than the more complex inorganic or organic compounds. Although certain complex iron salts, as for example ferrous gluconate, have been advocated in the belief that they are less apt to produce gastrointestinal upsets, it has been our experience that when these complex salts are administered in amounts sufficient to give a dose of iron comparable to that supplied by ferrous sulfate, gastrointestinal symptoms occur just as frequently as they do with ferrous sulfate.

Although iron is effective when given parenterally, it is practically impossible to give adequate amounts of the metal without producing serious and even dangerous symptoms. Nausea, vomiting and acute vascular collapse have followed the intramuscular injections of as small an amount of iron as 70 mg.⁷ In contrast to the hazard of iron administered by injection, orally administered iron does not produce systemic symptoms. Approximately one in three or one in four individuals may develop some type of gastrointestinal distress from a full dosage of iron given by mouth. These symptoms usually consist of cramps, gaseous distress and constipation or diarrhea. These distressing symptoms frequently may be avoided by beginning iron medication with a small dose (0.2 to 0.5 gm. of ferrous sulfate daily), and by gradually increasing the dose until the patient is receiving a full 1.5 to 2 gm. of ferrous sulfate. It is advisable to administer iron with meals or immediately following meals, since this tends to minimize gastrointestinal upsets. It is true that some of the iron administered with food probably forms insoluble and unutilized complexes, but from a practical standpoint this is not a major consideration, and the avoidance of the complication of enteric upsets justifies the slight loss in efficacy.

An occasional patient either will not or cannot (intestinal irritation, colostomy) take iron by mouth. In such individuals the anemia is probably best treated by blood transfusion. The transfusion of 500 cc. of blood supplies the equivalent of 260 mg. of iron, which, following the normal destruction of the transfused red cells, will enter into the general metabolic pool of body iron and be used for formation of the recipient's erythrocytes. In this fashion an amount of iron far greater than that which feasibly can be injected can be administered advantageously and safely. Our advocacy of transfusion as a means of administering iron by parenteral means is not to be interpreted as advising blood transfusion as a routine procedure in the treatment of patients with iron-deficiency anemia, since the vast majority of these patients respond quite satisfactorily to the oral administration of iron. Transfusion should be resorted to as a therapeutic measure in iron-deficiency anemia only in cases in which it is not possible to administer iron preparations by mouth.

The dosage of medicinal iron necessary to produce optimum blood regeneration varies widely from patient to patient and some patients may show maximum hematopoietic response only if three or four times the usual dose of 1.5 to 2 gm. of ferrous sulfate is administered. When a full therapeutic dose of iron is given to an individual with iron deficiency anemia, reticulocytosis occurs and hemoglobin regeneration proceeds at a rate of approximately 0.07 to 0.18 gm. per 100 cc. of blood daily.

The addition of so-called "accessory substances" to medicinal iron has recently received much publicity from drug manufacturers with the claim that more rapid, more complete and more lasting hemoglobin regeneration will be produced. Vitamins, copper, molybdenum and extracts of liver or stomach are most commonly advocated. About the only proven effect that any of these substances has is that of greatly increasing the price of the medication. Addition of members of the vitamin B complex to iron does not increase its utilization or improve the rate of response.⁸ The much advocated "Whipple secondary anemia fraction of liver" likewise fails to improve the effectiveness of iron in the treatment of iron deficiency anemia.⁹ Copper, originally shown to be effective in treating the anemia of milk fed rats,¹⁰ has never been shown to be of value in treating the anemia of adult human patients and the evidence for its effectiveness in the anemias of children is very equivocal.¹¹ Copper is widely distributed in natural food stuffs and is present as a contaminant of medicinal iron salts.¹² The minute amounts of copper required for human nutrition are certainly provided coincidental to iron therapy in any patient who is treated adequately for iron deficiency. Furthermore, the possibility exists of producing irreparable liver damage by the administration of copper.^{13, 14} In the present state of our knowledge, there is no reason for adding these various substances to medicinal iron, and very adequate reasons for not doing so. To prescribe proprietary preparations combining iron with these various accessory substances increases the cost of the medication five to twenty fold, and not infrequently may actually result in a decrease in the amount of iron provided the patient.

Practically the only exception to the statement that microcytic hypochromic anemia is always due to iron deficiency is the hereditary anemia occurring in members of the Mediterranean races, usually known as "Cooley's anemia," "Mediterranean disease," "thalassemia" or "familial erythroblastic anemia." In this condition extreme degrees of microcytosis and hypochromia exist, and yet the patients suffering from the condition show absolutely no response to medicinal iron. There is no known form of therapy which will produce an improvement in the morphologic characteristics of the erythrocytes and the only effective therapy is transfusion. Except for this group of cases however practically all cases of microcytic hypochromic anemia will

respond with hemoglobin regeneration and be cured if iron is administered in adequate amounts

NORMOCYTIC NORMOCHROMIC AND MICROCYTIC NORMOCHROMIC ANEMIAS

Pregnancy.—During the course of normal pregnancy, an anemia of moderate degree normally develops. It is characterized by erythrocytes of normal size and normal hemoglobin concentration, and the blood hemoglobin concentration rarely falls below 10 gm per 100 cc. This anemia is "physiological" and is supposedly due to an absolute increase in plasma volume. It is uninfluenced by administration of liver, iron or other medication, and requires no specific therapy. However, true iron-deficiency anemia of the microcytic hypochromic type is extremely common in pregnant women.^{3, 4} Indeed, it is so common that certain authorities have advocated the routine administration of medicinal iron to all pregnant women.^{3, 4, 15}

Acute Hemorrhage.—Immediately following hemorrhage, an anemia develops which will be of the normocytic normochromic variety, if the body stores of iron are adequate to allow hemoglobin regeneration. In such cases, it is advisable to administer iron in order to replenish the body stores.

Hemolytic Anemias.—The hemolytic anemias (e.g., familial hemolytic jaundice and paroxysmal nocturnal hemoglobinuria) are characterized by erythrocytes which are either normal or increased in size, and which have a normal cellular concentration of hemoglobin. They are further distinguished by the increased numbers of reticulocytes which are constantly present in the peripheral blood. The treatment of hemolytic anemias must be directed at removing the underlying and contributing causes of the increased hemolysis, and in preventing the anemia from becoming so severe as to hazard the patient's life. In familial hemolytic anemia the severity of the hemolytic process can be markedly reduced by splenectomy, which will usually produce marked clinical improvement in patients with the disease even though it does not remove the underlying abnormality of the erythrocytes. In paroxysmal nocturnal hemoglobinuria and other types of hemolytic anemia, splenectomy may be of no value. When the hemolytic process progresses very rapidly or is so severe that dangerously low levels of blood hemoglobin (5 to 6 gm per 100 cc of blood) are reached, blood transfusions must be given. In our experience, transfusions of red blood cells separated from their plasma are more efficient in raising hemoglobin levels than transfusions of whole blood. When such red cell suspensions are used, the volume of fluid to be transfused is only one-half as great as the volume of whole blood necessary to provide the same amount of hemoglobin, and the rapidity with which the red blood cell count can be restored to normal can be greatly increased.

Systemic Diseases.—Normocytic normochromic and microcytic normochromic anemias are encountered in various serious systemic diseases, the anemias supposedly being caused by a "toxic depression" of bone marrow activity. Chronic infections, severe renal disease and widespread malignancy are the most common causes of this "toxic depression." In cases in which the bone marrow is aplastic or is crowded out by tumor the erythrocytes usually are normal in size and hemoglobin content. Such cases are benefited by transfusions of red blood cells, which are to be regarded as a "stop gap" measure to tide the patient over periods of very low hemoglobin levels. Other specific therapy of these anemias is of no value. Attempts should be made to discover and remedy the underlying cause of inhibition of the bone marrow.

MACROCYTIC ANEMIAS

Since Minot and Murphy¹⁶ demonstrated the effectiveness of liver in the treatment of pernicious anemia, the concept that most macrocytic anemias are due to some type of deficiency disease has gradually gained credence. This concept has recently gained strong support from the discovery of the beneficial effect of the *Lactobacillus casei* factor ("folic acid") in Addisonian pernicious anemia, in "nutritional macrocytic anemia" and in the macrocytic anemia of sprue. It seems probable that other specific chemical substances will be found to be effective in types of macrocytic anemia which show no response to known therapeutic agents.

Pernicious Anemia—Addisonian pernicious anemia, by far the most common type of macrocytic anemia in most regions of the United States, is, fortunately, the one which responds most satisfactorily to liver extract therapy. Although orally administered whole liver or liver extracts will produce remission with return of the blood to normal, this mode of treatment is not to be recommended. Most individuals rapidly gain a dislike for the amount of liver (400 to 500 gm daily) which must be taken by mouth to maintain remission, and the cost of treatment taken in this way is very high. Liver extract given by intramuscular injection is 60 to 100 times more effective than when ingested, and is far less expensive.¹⁷ The use of highly purified liver extracts has been shown to be just as adequate as crude extracts in the control of neurological and hematological symptoms¹⁸ and the 15 units per cc. concentrate, in addition to being fully effective therapeutically is tolerated far better by the patient than are the larger volume crude extracts. In treating a patient with pernicious anemia in relapse it is advisable to administer 15 units of liver extract daily for a period of ten days, and then to give 30 units per week in single injections for a period of two months. At the end of this time, the blood should have returned to normal progress of neurological signs and symptoms should be arrested, and gastrointestinal symptoms should be completely

relieved, although gastric achlorhydria will persist unchanged. The majority of patients can subsequently be controlled with a single injection of 15 or 30 units of liver extract once a month. The amount of liver extract administered should be adjusted to the requirements of each patient and should be adequate to maintain a normal blood picture and to prevent recurrence or progression of neurological symptoms. Some cases may require as much as 50 or 75 units each two to four weeks to achieve this goal.

The accuracy of the diagnosis of pernicious anemia and the effectiveness of the liver extract therapy should always be confirmed by demonstrating a reticulocyte response five to ten days after the initial injection of liver extract. In the absence of such a response, the diagnosis must be considered in error, or the liver extract not potent.

The complications resulting from bringing a case of pernicious anemia into remission by liver extract therapy are few and infrequent. Previously existing hypertension rarely may be aggravated by the increase in blood levels. Thrombosis and embolism, particularly in coronary and cerebral vessels, occasionally may occur, presumably as a result of the increase in blood platelets. The increase in activity permitted by the clinical improvement of these patients, and the fact that they are usually in the older age group, contribute to an increased incidence of cardiovascular complications following therapy.

Reactions to liver extract administered intramuscularly are infrequent. When they occur, the large majority appear to be on a true allergic basis. Skin tests indicate that this sensitivity is due to some substance in liver extract itself, irrespective of its biological source (hog, beef, etc.)^{19, 20} This allergy differs from atopy, however, in that there is no constancy in the reaction of a patient to liver, and one cannot predict when an allergic reaction will develop or fail to develop. Most patients have their first reaction after numerous well-tolerated injections and then never have another, even though they receive the same brand and the same quantity of liver extract. This occurs particularly after a long injection-free interval. Some patients have reactions interspersed with reaction-free intervals. The clinical manifestations are extremely varied, and include practically every allergic sign and symptom, although local reactions and urticaria are the most common findings. Substernal oppression, dyspnea, tachycardia, sweating and a fall in blood pressure sometimes occur, as do angioneurotic edema, asthma and eosinophilia. Although immediate reactions may be severe, no fatalities have been reported.

The symptomatic treatment of allergic reactions to liver extract consists of subcutaneous injection of 1 to 5 minims of adrenalin and local symptomatic treatment of itching. Changing the brand of the extract and the dose rarely has any effect on the occurrence of reactions, and changing to oral preparations may or may not help in avoiding reac-

tions Desensitization with gradually increasing doses of diluted liver extract is recommended for patients who react frequently, and is usually, although not always, successful. After desensitization, therapeutic injections should be continued at least once a week in order to keep the patient "desensitized." Folic acid offers a solution to the occasional cases in which desensitization is unsuccessful.

Patients with pernicious anemia who have exhibited a clinical response to liver extract and who have subsequently relapsed during regular and adequate parenteral liver extract therapy are extremely rare. Such an event almost always indicates the onset of some other distinct disease process or complication, not infrequently a neoplasm of the gastrointestinal tract. The incidence of carcinoma of the stomach in patients with pernicious anemia is far greater than in the general population. Kaplan and Rugler²¹ reported a study of 23,231 autopsies on individuals over forty five years. Two hundred and ninety three cases of pernicious anemia were found, thirty six of these 293 patients also had carcinoma of the stomach, an incidence of 12.3 per cent, which is over three times as great as the incidence in the remaining autopsy population of the same age. In clinical studies the incidence of gastric neoplasm in patients with pernicious anemia also has been found to be considerably in excess of the usual incidence.^{22 23} Unequivocally these statistics indicate that there is a relationship between pernicious anemia and carcinoma of the stomach. We believe that all patients with pernicious anemia should have thorough radiographic examination of the upper gastrointestinal tract at least once a year. Such examinations will frequently demonstrate a gastric neoplasm early enough so that successful operative removal may be performed. Macrocytic anemia caused by carcinoma of the stomach has been reported,²⁴ but is extremely rare. A few cases of macrocytic anemia following gastric resection have been recorded in the literature.^{25 26 27} These cases respond to liver extract therapy, although large doses are sometimes required.

Sudden failure of an occasional patient with Addisonian pernicious anemia to respond to adequate amounts of parenteral purified liver extract in the absence of factors known to interfere with a therapeutic response has been observed in a few instances.^{28 29 30} Davidson²⁸ has employed blood transfusions to overcome the refractory state and Mulholland²⁹ has reported one case in which intravenous liver extract resulted in a prompt and complete remission. Choline chloride was used successfully in one instance by Moosnick, Schleicher and Peterson.³⁰ This case, however, was demonstrated to have fatty metamorphosis of both the bone marrow and liver which was apparently benefited by the lipotropic action of choline. The authors suggest that choline chloride or substances containing choline be used to supplement liver extract when a fatty state of the liver or bone marrow, or both, is present,

particularly when a progressive anemia develops during administration of adequate liver extract therapy. There is no justification for the use of choline chloride or similar lipotropic substances in cases of macrocytic anemia showing no fatty metamorphosis of bone marrow or liver. Choline hydrochloride has been found completely ineffective in patients with nutritional macrocytic anemia.³¹

Many substances have been studied in an attempt to find the active principle of liver extract. Among these materials is the so-called Lactobacillus casei factor ("folic acid"), a substance known to be essential for the growth of certain bacteria³² and for the prevention of macrocytic anemia in chicks.³³ In 1945, reports began to appear of the therapeutic effectiveness of synthetic L. casei factor in nutritional macrocytic anemia,³⁴ in pernicious anemia in relapse³⁵ and in the macrocytic anemia of sprue.³⁶ Of these three syndromes, sprue appears to be most strikingly benefited. Fifteen milligrams of synthetic L. casei factor daily will rapidly produce clinical "cure" in many cases and restore the blood picture to normal. How completely the intestinal malfunction and abnormality in fat metabolism will be controlled is not yet established, but it appears quite certain that synthetic L. casei factor is the most effective agent yet used in the treatment of sprue.^{37, 38}

The practical value of L. casei factor in the control of pernicious anemia is not yet so certain. Most of the cases of pernicious anemia treated with the synthetic L. casei factor have shown a reticulocyte response and have regenerated erythrocytes,^{35, 39} but in several patients the reticulocytosis has been submaximal and blood regeneration has ceased before normal erythrocyte and hemoglobin levels were attained. Furthermore, nothing is known concerning the effectiveness of L. casei factor in controlling combined system disease, the most serious aspect of pernicious anemia. A great deal more investigative work must be done before it will be possible to state the proper role of L. casei factor in the control of pernicious anemia. At the present time liver extract still remains the agent of choice.

The L. casei factor has been chemically identified as N-[4- { [(2-amino-4-hydroxy-6-pteridyl) methyl] amino benzoyl] glutamic acid ("pteroylglutamic acid")^{39a} and synthesized in large amounts, but its mode of action in promoting blood formation is still unknown. It seems quite certain that it is not the extrinsic factor of Castle since it is effective when injected parenterally. It is not the active principle of liver extract, since potent purified liver extracts contain only infinitesimal amounts of L. casei factor, and the latter substance is effective only in relatively large amounts.

Two other compounds recently have been announced to be effective in certain macrocytic anemias. Scott and his associates^{40, 41} have shown that the macrocytic anemia which develops in chicks fed a purified diet or which follows hemorrhage is benefited by either L. casei factor or

the acid or lactone forms of 2-methyl-3-hydroxy-4-hydroxymethyl-5-carboxypyridine (α pyracin) and its isomeric 4-carboxy form (β pyracin). Moreover when these factors are administered together, anemia in chicks responds much more rapidly and the blood reaches higher levels than when either factor is administered alone. Clinical investigation of this material in humans has not been carried out. Spies^{42, 43} has recently reported that thymine (2,4-dioxo-5-methyl pyrimidine) is a potent anti pernicious anemia factor when administered in large amounts. He suggests the interesting hypothesis that the L. casei factor may act as an enzyme or coenzyme in the synthesis of thymine, which is an integral constituent of living cells.

Nutritional Macrocytic Anemia and the Pernicious Anemia of Pregnancy—A hematologic picture similar to that of Addisonian pernicious anemia occurs in the macrocytic anemia of extreme nutritional deficiency,⁴¹ and in the pernicious anemia of pregnancy.⁴⁴ However in contrast to Addisonian pernicious anemia, free hydrochloric acid is usually present in the gastric secretions of these patients. Both of these types of anemia usually respond to parenteral injection of purified liver extract, but some cases are completely refractory to such treatment. Wills⁴⁵ found that some of these cases would respond to injections of crude liver extract or to the oral administration of autolyzed yeast. Recently Watson and Castle⁴¹ showed that these patients might be divided into two groups. The first group responded to large amounts of crude liver extract given either by injection or by mouth and the second group responded only to orally administered crude liver extract. Sometimes as much as fifty times the usual parenteral dose of liver extract had to be given by mouth in order to bring about remission. Once the anemia has been overcome, maintenance therapy usually is not necessary provided that the dietary deficiency is corrected or the pregnancy terminated.

Another group of macrocytic anemias refractory to purified liver extract and with free hydrochloric acid in the gastric juice have occasionally been called "achrestic" anemias. Davis and Davidson⁴⁶ have reported that some of these cases may respond to orally administered papain digest of whole liver. In our experience this preparation was ineffective in producing remission in patients who would not respond to injections of adequate amounts of purified liver extract. Whether or not such patients will be found to respond to L. casei factor is unknown. Watson and his collaborators⁴⁷ have reported that the L. casei factor was ineffective in relieving certain cases of "aplastic" anemia. Some patients with advanced cirrhosis of the liver develop a macrocytic anemia which will show only a limited response to purified liver extract. Occasionally further improvement has been produced when crude liver extract was administered by mouth. Several of these cases have shown no response to L. casei factor.

SUMMARY AND CONCLUSIONS

Anemia is usually a reflection of an underlying abnormality—e.g., chronic blood loss, nutritional deficiency, or severe systemic disease. In the treatment of anemia it is absolutely necessary that the nature of the underlying disease process be determined and an attempt be made to remove its cause. The anemia itself will respond to specific therapy in the majority of cases.

Classification of anemia on the basis of erythrocyte morphology is of great aid in suggesting the probable nature of the underlying disease process and in indicating the appropriate specific therapy.

Microcytic hypochromic anemia (with the exception of the hereditary Cooley's anemia) develops as a consequence of iron deficiency and is commonly a reflection of chronic blood loss, growth or pregnancy. The source of blood loss must always be located and eradicated. This type of anemia responds to the oral administration of adequate amounts of medicinal iron in the form of simple ferrous salts. The addition of liver extract, vitamins, copper and other "accessory substances" has no proven beneficial effect in promoting blood regeneration.

Normocytic normochromic and microcytic normochromic anemias usually are a reflection of a serious underlying systemic disease, and treatment must be directed at the underlying pathological process. In such cases blood transfusion may be used as a palliative measure to maintain satisfactory hemoglobin levels.

Most cases of macrocytic anemia are due to some type of deficiency and will respond to liver extract or to *Lactobacillus casei* factor ("folic acid," "pteroylglutamic acid"). At present, parenterally administered purified liver extract is the therapeutic agent of choice in Addisonian pernicious anemia, and orally administered *L. casei* factor is the most effective agent in the treatment of the anemia of sprue.

In conclusion, we would like to emphasize again the importance of establishing the correct diagnosis of the type of anemia, and the absolute necessity for determining the cause of the anemic state before treatment is instituted. The great majority of anemic patients will show excellent response to simple specific therapeutic measures properly employed. The use of all-inclusive "shot-gun" remedies must be condemned as a meddlesome practice.

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CORONARY OCCLUSION

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OCCLUSION of a coronary artery may result from a variety of pathological processes. By far the most common direct cause is clotting of blood, or coronary thrombosis. Invariably this clotting occurs in a diseased vessel, usually the site of atheromatous degeneration, but other pathological processes may provide the nidus for clotting. Collateral factors, some known or suspected and others unknown, are probably important adjuncts. Of the known or suspected additional factors, the most important are increased coagulability of the blood and inordinate slowing of coronary blood flow. In a patient with moderately advanced disease of the coronary arteries, these collateral factors may, on occasion, be important contributing causes of coronary thrombosis. The slowing of blood flow may be brought about by, for example, an increase in blood viscosity (polycythemia or hemoconcentration) or by shock or serious fall in blood pressure from any cause.

The subject of increased coagulability of the blood has only recently received attention. The more dramatic hemorrhagic diseases have been studied extensively, but the opposite state of affairs, increased coagulation, has heretofore been neglected. The field is largely unexplored, but, by studying blood coagulability by determination of prothrombin time on diluted plasma or in serial dilutions of heparin, it has been shown that bed rest after an operation or illness increases the coagulability of the blood. It is probable also that some individuals have an inherent tendency to hypercoagulability, although the evidence at hand from studies on patients with coronary thrombosis seems to indicate that an inherent tendency to clotting, as measured by prothrombin time on diluted plasma, is not a striking feature in these cases.¹

The knowledge that neither slowing of blood flow nor increase in coagulability of the blood is recognizable in the majority of patients with coronary thrombosis in no way detracts from the contention that some factor other than disease of the coronary arteries alone may be of importance in some cases. In the observation of routine autopsies on noncardiac cases one is often struck by the advanced coronary artery disease encountered without evidence of thrombosis being found.

Some of the other, less common, causes of coronary occlusion are

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obliteration of the lumen by subintimal hemorrhage, syphilitic involvement of the ostia generalized obliterative vascular disease (periarteritis nodosa, thrombo-angitis obliterans, and perhaps occasionally rheumatic fever) occlusion by debris from atheromatous plaques or abscesses, and, rarely, embolism. This last is usually due to bacterial endocarditis of the aortic valve or, rarer still to air or fat embolism. Effort may be a factor in the production of occlusion in some of the cases in this category for example, in occlusion due to subintimal hemorrhage or rupture of an atheromatous abscess.

No attempt has been made to exhaust the possible causes of coronary occlusion but enough has been said to make the point that coronary occlusion and coronary thrombosis are not always synonymous. A more important distinction is that neither term is synonymous with myocardial infarction. Occlusion of a coronary artery may occur without infarction of the heart, and infarction may occur when the coronary blood flow is decreased or when the metabolic needs of the heart are unduly increased, without any fresh occlusion of a vessel.

TREATMENT

Consideration of the pathology involved indicates that little or nothing can be done in the way of treatment of the occlusion itself. Indeed, in the absence of infarction it is difficult, and often impossible, to make a diagnosis of coronary occlusion. The fever, leukocytosis, electrocardiographic changes, increased sedimentation rate, gallop rhythm, friction rub, are all manifestations of infarction and are not produced by occlusion alone. The main body of this discussion will, therefore, be concerned with the treatment of myocardial infarction.

Immediate Treatment.—The two immediate problems to be dealt with in a patient who has had an acute myocardial infarct are the control of pain and decision as to the advisability of moving the patient either to a hospital, to his home, or even into another room. Pain is usually controlled by adequate doses of opiates. Morphine can be given subcutaneously or intramuscularly in an initial dose of $\frac{1}{4}$ or $\frac{1}{2}$ grains and repeated in half an hour if necessary. Dilaudid ($\frac{1}{16}$ grain) has the advantage of causing less nausea and vomiting than morphine and is, therefore, preferable. After the first twenty-four to forty-eight hours the control of pain is usually no longer a problem and the opiates can be eliminated. In some refractory cases the administration of oxygen may relieve pain which is uncontrolled by opiates.

The admonition, commonly heard, that a patient with acute myocardial infarction must not be moved is overemphasized and, certainly in some cases, is carried to ridiculous extremes. Such a patient should not be allowed to undertake much under his own power, of course, but it seems doubtful that transportation in the proper manner does harm.

Diet and Rest.—For the first few days the diet should be light, preferably liquid. Many patients will benefit by weight reduction, and a dietary directed toward that end will not only produce reduction in weight but will considerably diminish the work of the heart. The bowels can be neglected for the first few days. An enema, or a gentle laxative, may be given on the third or fourth day and as needed thereafter. In this connection, also, the dictum of strictly enforced rest should be balanced by common sense. In uncomplicated cases there is no harm in allowing the patient to use a bedside commode, or even to walk a few steps to the bathroom, as it probably entails less effort than does precarious balancing on a bed-pan.

The length of time during which the patient is kept in bed will depend on the size of the infarct and the presence or absence of complications. The height and duration of fever and leukocytosis are fairly reliable guides to the size of the infarct, the sedimentation rate and electrocardiograms are less reliable. A patient who has, for example, a temperature of 100° F for a day or two and, perhaps, a white blood cell count of 12,000 to 15,000 for three or four days, can be considered to have had a small to moderate-sized infarct. In the absence of complications, he can be allowed out of bed after the third, or certainly after the fourth, week. Larger infarcts or the presence of complications will require more prolonged rest.

Such a patient can then be allowed gradually increased activity for the next month and should be back at work by the end of the third month, provided that the work is not strenuous. The dictum of at least six weeks in bed and marked restriction of activity for six months to a year for *all* cases of myocardial infarction is not only unnecessary but is to be deplored. In many cases such a program goes far toward producing irreparable invalidism and mental depression, a complication not easy to deal with, once established.

Drug Therapy.—Aside from analgesics and sedation as needed, drug therapy plays a relatively small role in the uncomplicated case. The oral administration of aminophylline has its advocates, but it is doubtful that anything useful is accomplished by it.² There is experimental evidence that both atropine and papaverine^{3, 4, 5} have favorable actions on the unoccluded coronary vessels—preventing the generalized spasm of the coronary tree which occurs with experimental ligation of one of its limbs. Whether they have a similar action in a patient is unknown. All these drugs may have disagreeable, but seldom hazardous, side effects.

The dose of aminophylline should be 0.2 gm (3 grains) by mouth three or four times a day. When used in this amount it frequently produces gastric discomfort. Atropine in $\frac{1}{75}$ or $\frac{1}{100}$ grain doses may be given subcutaneously every four hours. If it has any usefulness, that usefulness is usually ended after the first forty-eight to seventy-two

answer is not known, but for the present its routine use had best be omitted until carefully evaluated studies are available.

The nature of the disease and the mechanism of the "shock" make failure of any treatment to be expected in many cases.

A word should be included concerning the fall in blood pressure which is a natural result of sedation and bed rest. The level of the blood pressure in the later stages of convalescence need not be given consideration in arriving at a decision to allow the patient out of bed. This seems an obvious principle, yet many patients have been kept in bed unnecessarily, awaiting return of their blood pressure to normal.

Congestive Heart Failure—A number of patients have congestive failure made worse or precipitated by myocardial infarction. The treatment does not differ significantly from that applied to patients with failure from other causes. *Digitalis* should be used in the same manner as in other cases, save that more than usual care should be taken to avoid toxic amounts. For the average-sized adult the "digitalizing" dose is approximately 1.2 to 1.5 gm. of the powdered leaf. This is best given in the dose of 0.1 gm. ($1\frac{1}{2}$ grains) three times a day for five days. Rarely is more rapid digitalization necessary. Thereafter a maintenance dose of 0.1 gm. either daily or for six days a week usually suffices.

Restriction of fluids and sodium salts and the use of diuretics are indicated. The xanthine diuretics, such as aminophylline or theobromine, may be effective enough, or the more powerful mercurials may be needed. The possibility of fatal reactions from the intravenous use of the mercurials is probably greatest in this group of patients, and intramuscular administration is preferable. Two misconceptions, not limited to this group of patients, are commonly encountered in relation to the use of diuretics. One is the failure to appreciate the need for diuretics in patients with pulmonary congestion but without peripheral edema, and the other is the fear of mercurials when abnormal urinary findings and/or elevation of the blood urea or nonprotein nitrogen are present. When these findings are present they are often due to the congestion itself, and the use of diuretics will clear the abnormalities. The nonprotein nitrogen may be as high as 100 mg. per 100 cc., or more, due to congestion alone. A helpful point in distinguishing between nitrogen retention due to congestion and that due to kidney failure is the specific gravity of the urine. So long as the kidneys are able to concentrate urine of a specific gravity of 1.020 or more under these circumstances, the mercurial diuretics may be used.

Arrhythmias—Various types of conduction defects or ectopic rhythms may result from cardiac infarction. Of the conduction defects the only one needing treatment is auriculoventricular block with Adams-Stokes attacks. Treatment of an attack itself consists of the use of aqueous epinephrine intravenously or directly into the heart in a

dose of 3 to 5 minims. Such heroic measures, however, rarely can be considered life-saving, for if the heart has not resumed beating by the time the drug can be given and take effect it is unlikely ever to do so. Furthermore, if possible, one should be certain that the cessation of heart action with resulting coma or convulsion is, in fact, due to heart block rather than to ventricular fibrillation. Epinephrine is contraindicated in the latter arrhythmia. Once a patient has had an Adams-Stokes attack it is important to institute treatment aimed at the prevention of future attacks. If possible, electrocardiographic proof of the mechanism should be obtained. If block is demonstrated, or if it seems to be the likely mechanism, epinephrine in oil (0.5 cc.) may be used intramuscularly every three hours or more often if necessary. Ephedrine sulfate ($\frac{3}{8}$ grain) may be given by mouth either in conjunction with epinephrine in oil or alone. Its action is less dependable than epinephrine, but it may be used for a time after the acute period of attacks has subsided. The length of time over which such attacks occur usually is limited to a few days or a week or two, as the cardiac mechanism tends to stabilize at some type of supraventricular rhythm or at complete block. Attacks rarely occur when the block has become complete and the block itself needs no treatment. Occasionally digitalis may be used to bring about complete block, and so abolish the attacks, when the duration of varying block is prolonged. Other measures sometimes advocated, such as the use of barium chloride, atropine, or thyroid extract, are of less value than epinephrine or ephedrine.

Any of the ectopic rhythms may occur with infarction, and all are worthy of therapeutic attention. Premature beats, either auricular or ventricular in origin, should be treated because, if frequent, they interfere with adequate function of the heart, and because they may presage the more serious ectopic rhythms. Quinidine sulfate (0.2 gm.) may be given three or four times a day and in this amount it usually will control premature contractions. If necessary twice that amount may be used preferably under electrocardiographic control to avoid toxic manifestations.

Paroxysmal tachycardia of either supraventricular or ventricular origin may occur. The latter is the more important type because it may eventuate in ventricular fibrillation. When, however, auricular or nodal tachycardia occurs with cardiac infarction, it assumes more importance than a similar attack in normal persons as the rapid rate may impose considerable strain on the damaged heart. Auricular tachycardia can often be terminated by holding the breath or by ocular or carotid sinus pressure. If these measures fail quinidine should be used.

The method of using quinidine is essentially the same in cases of auricular or ventricular tachycardia, and paroxysmal auricular flutter or fibrillation. Several methods have been suggested, but the one with the least danger of intoxication is as follows: Six grains of quinidine

sulfate are given by mouth every two hours under electrocardiographic control. That is, just prior to each dose an electrocardiogram should be made and interpreted. If either intraventricular or supraventricular block develops, succeeding doses should not be given. Since a single dose of quinidine is not wholly excreted until after four hours, the practice of giving a dose every two hours results in a gradually increasing concentration of the drug. Unless conditions seem extremely urgent, no more than six such doses should be given in any one course. When congestive heart failure occurs, digitalis may be used in the usual amounts, and may be the drug of choice, even in the absence of failure, in treating auricular fibrillation or flutter. It should not be used in the presence of ventricular tachycardia. In urgent cases quinidine sulfate can be given intravenously in a dose of 0.6 gm dissolved in 250 cc of sterile physiological saline solution. It should be given slowly. After the rhythm has returned to normal, quinidine should be given by mouth for a week or ten days in order to prevent a recurrence of the abnormal rhythm. Usually 0.2 gm four times a day will suffice to accomplish this end.

If quinidine fails to control paroxysmal tachycardia or if a contraindication to quinidine exists, such as known sensitivity to quinine products or the antecedent demonstration of some degree of heart block, magnesium sulfate intravenously may be used. The dose is 20 cc of a 10 per cent solution.

Vascular Complications—These are among the most frequent and most important complications of myocardial infarction.⁷ Peripheral or cerebral emboli arising from intramural thrombosis, at best, increase the length and degree of disability and, at worst, may cause a fatality where otherwise a good recovery might occur. Pulmonary emboli, usually arising from the deep veins of the legs, less often from other veins, and rarely from intracardiac thrombosis, may kill the patient when the cardiac infarct has almost, or entirely, healed. Extension of the thrombus in a coronary artery is a possible additional vascular complication, although it is uncertain how important this possibility is. It is apparent that a safe anticoagulant could prevent many such complications and even, in some cases, death. Dicoumarol has been suggested and used in a series of cases with material reduction in morbidity and mortality.¹ According to investigators reporting the use of dicoumarol, it is safe when properly controlled.

One simple expedient that can be used in most patients which will help to prevent pulmonary emboli—and this is by far the largest group—is early exercise of the leg and calf muscles to aid the venous return and prevent stasis. Such exercise can be started after the first few days and need not be strenuous to accomplish results. Merely pressing the feet against the foot of the bed at intervals during the day, along with deep breathing, which also aids venous return, will suffice.

MENTAL REHABILITATION

The subject of treatment of myocardial infarction should not be left without emphasizing the need for mental rehabilitation of the patient. This was implied earlier while dealing with the length of time the patient should be kept in bed and as an invalid. It should be re-emphasized here that an optimistic, cheerful outlook is both justifiable and desirable. Less than 20 per cent of patients die in the first attack, and the average length of life following the first attack is approximately five years—a record considered good in the field of surgical attack on malignant disease. Many patients live much longer and life should have breadth and depth, as well as length. With these thoughts in mind, what advice should be given to the patient who has recovered from myocardial infarction? How active may he be? Some causes of coronary occlusion are, or may be, precipitated by effort, such as subintimal hemorrhage. Others may be brought on by rest, for example, thrombosis due to slowing of blood flow. It is certain that about as many attacks occur at rest as on effort, and there is no more justification for interdicting all exertion than for prohibiting all rest. Sudden extreme effort, or sustained effort, should not be indulged in, but many patients can lead a normal, quiet life—walking, stair-climbing, golf, or other mild exercise. Those whose recovery is less complete and who are left with angina pectoris or congestive failure may and probably will, need more rigid restriction. A safe rule to follow in such patients is to allow those activities which do not give rise to chest pain or breathlessness. The presence of symptoms, not functional in origin, will determine how nearly normal his life may be.

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DIAGNOSIS AND TREATMENT OF THROMBO EMBOLIC DISEASE

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DEATH from massive pulmonary embolism is still a serious threat to a patient's life following major surgical operations, trauma of the lower extremities, protracted serious illnesses and pregnancy. The relationship between venous thrombosis of the lower extremities and pulmonary embolism is well established. It is believed that the source of at least 95 per cent of pulmonary emboli is to be found in the deep veins of the legs. The thrombotic process originates in the veins of the calf muscles, tributaries of the posterior tibial and peroneal veins. From these vessels the thrombosis extends into the popliteal and femoral and sometimes the iliac veins. In many instances the thrombus is not adherent to the vein wall, so that portions of it may break off to produce pulmonary embolism. The importance of the realization that the majority of pulmonary emboli both minor and lethal originate in the deep veins of the lower extremities cannot be overemphasized, since it is only by prophylactic measures to prevent thrombosis in these vessels and by the early diagnosis and treatment of venous thrombosis that the mortality rate from pulmonary embolism can be reduced.

Numerous terms have been used in the literature to describe the phenomena of venous thrombosis, such as thrombophlebitis, phlebothrombosis, bland or silent venous thrombosis, or just plain venous thrombosis. The underlying basic pathology is the same in all of these. The degree of pain and swelling usually depends on the extent to which the venous return from the limb has been blocked by the thrombosis. Extensive clot formation may be present with minimal signs of pain or swelling. This type, for which Ochsner has popularized the term "phlebothrombosis," results in fatal embolism since the thrombus for the main part is unattached to the vein wall and if dislodged may lodge in the pulmonary artery to produce sudden death. It is less likely to occur where there is marked swelling and venous congestion of the entire leg, because the thrombus is usually adherent to the vein wall throughout its entire extent. Nevertheless, even under these conditions, fatal pulmonary embolism has been observed. It is believed that irrespective of whether the thrombosis is localized only to the calf veins,

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measures should be taken to prevent the dislodgment of the thrombus with resulting pulmonary embolism. There is little if any evidence that a thrombosis is secondary to infection, since repeated attempts to culture bacteria from the thrombi have been unsuccessful, so that chemotherapy is not indicated in the usual case.

PROPHYLAXIS

The prevention of deep venous thrombosis and pulmonary embolism cannot be accomplished in all patients, but the incidence can be reduced if certain measures are taken. The early ambulation of patients, even after major abdominal operations is an important prophylactic measure. Abdominal incisions should be sutured so that patients may get out of bed the first or second postoperative day. If the patient is allowed up it is extremely important that he should be made to walk but not allowed to sit in a chair for at least a week since sitting tends to produce venous congestion with resulting thrombosis. There is much to recommend early ambulation but it is important to remember that it will not prevent all cases of venous thrombosis and pulmonary embolism, since the condition is seen occasionally in patients who have not been in bed for operation or illness. For this reason examination of the extremities in early ambulation patients should still be carried out at frequent intervals.

For those patients who cannot be mobilized early, it is believed that the best position for the bed is with its head elevated by means of blocks under the bed posts so that the patient is lying on a slight incline. A wide board is placed at the foot of the bed so that as the patient tends to slide downward he can push against it with his feet. This results in exercise and contraction of the calf muscles thus favoring the emptying of the veins, where it is generally conceded that thrombosis originates. Every effort should be made to encourage the patient to move around in bed and to exercise his legs. Tight abdominal binders should not be used since they tend to increase intra-abdominal tension with interference of the venous return from the lower extremities. Elevation of the bed under the knees or placing of pillows in this region should not be permitted, as this may also favor stagnation and thrombosis.

At the present time it seems advisable to recommend that the anti-coagulants, heparin and dicumarol, be used only as prophylactic therapy since in our Clinic after thrombosis of the deep veins of the legs has been recognized both fatal and nonfatal pulmonary embolism have occurred with this type of treatment. We are studying a series of cases in which dicumarol is being used prophylactically, in an attempt to evaluate the efficacy of this drug but it is too early to evaluate the results. There are however a number of favorable reports in the literature in which this method of prophylaxis was employed.

Another prophylactic measure which deserves attention is bilateral interruption of the superficial femoral veins in patients who are apt to develop venous thrombosis and pulmonary embolism. It has been shown from a statistical study that venous thrombosis and pulmonary embolism occur most frequently in postoperative patients who are over 40 years of age and that the sudden massive fatal embolus occurs most frequently without warning from thrombosis in patients over 60 years of age. It has also been shown that a higher incidence of fatal pulmonary embolism occurs in patients following operations for abdominal carcinoma than in almost any other group. For these reasons it seems a justifiable procedure to carry out bilateral interruption of the superficial femoral veins in any patient 50 years of age or over, who is subjected to major abdominal or pelvic operations for malignancy. We have carried this out in over 200 patients and so far none has developed venous thrombosis or pulmonary embolism when the vein interruption was properly performed. The operation may be done in connection with the major abdominal procedure, or if the surgeon so desires as a separate procedure, preferably before the major operation. It is also recommended in patients subjected to open reduction of intertrochanteric fractures of the femur.

DIAGNOSIS

The early diagnosis of deep venous thrombosis is important in the prevention of fatal pulmonary embolism. Swelling of the leg with local tenderness was observed to be the most common objective sign of deep venous thrombosis. In an analysis of 500 cases this was found to be present in 66 per cent. Discomfort in the calf or popliteal regions on forceful dorsiflexion of the foot, the sign described by Homans, was present in 41 per cent. Minor pulmonary embolism surprisingly was the first clinical evidence, in 35 per cent of the cases, that venous thrombosis existed. In cases in which a suspicion of pulmonary infarction or embolism is aroused, anteroposterior and lateral roentgenograms of the chest should always be taken. The sudden development of severe pleuritic pain, followed by hemoptysis, is almost pathognomonic of pulmonary infarction. The concomitant rise in temperature, pulse and respiration in a patient with a preceding normal chart is a valuable sign, as it frequently indicates the lodgment of a small pulmonary embolus. In doubtful cases the electrocardiogram may be a valuable aid in differentiating between pulmonary embolism and coronary thrombosis. The visualization of the deep venous circulation to the lower extremities by phlebography has been given up as a routine procedure, because the interpretation of the phlebograms is difficult especially in the early cases. One of our patients with bilateral normal phlebograms died two days later of massive pulmonary embolism.

TREATMENT

Conservative Treatment—The method of treating deep venous thrombosis by rest in bed and elevation with the application of ice or hot packs should no longer be acceptable except in the unusual case. It necessitates a long period of hospitalization and at the same time it does not protect the patient from the dangers of pulmonary embolism. The same objection can be said of the injection of the lumbar ganglia with procaine solution, which gives symptomatic relief both as regards pain and swelling but does not eliminate the danger of pulmonary embolism. The anticoagulants, heparin and dicumarol, in our experience are more useful in the prophylactic treatment than they are in the definitive treatment once deep venous thrombosis with or without pulmonary embolism has occurred. After the drug has been discontinued, both minor and fatal pulmonary emboli have been observed in our cases so it is difficult to know how long the therapy should be continued, especially in the patient who is chronically ill and must be kept in bed for a long period of time.

The Surgical Treatment of Deep Venous Thrombosis—The interruption of the femoral vein at the groin is an accepted method to prevent fatal pulmonary embolism. It was first described by Homans in 1934. Since 1937 over 1000 patients at the Massachusetts General Hospital have either had one or both femoral veins interrupted. In our opinion it is a simple and safe procedure that may be carried out on very ill patients without serious detrimental effect to the extremities. The anesthesia of choice is local infiltration of 1 per cent procaine solution. It is our opinion that the femoral vein in both legs should be interrupted even if a diagnosis of deep venous thrombosis is made in only one extremity. This is because fatal pulmonary embolism has occurred from the unsuspected leg and also deep venous thrombosis may develop in the unligated leg, necessitating a second operation. The chief indications for bilateral femoral vein interruption are (1) the presence of deep venous thrombosis of the lower extremity (2) the occurrence of a nonfatal pulmonary embolus irrespective of whether or not the legs show signs of venous thrombosis (3) a concomitant rise in temperature, pulse and respiration in a patient with a previously normal chart that cannot be explained by some other cause, and (4) it is believed that prophylactic bilateral femoral vein interruption is a justifiable procedure in patients over 50 years of age who are subjected to major abdominal or pelvic operations for malignant disease. This procedure is also recommended in elderly patients who have an open reduction of intertrochanteric fractures of the femur because this group of patients show a very high incidence of fatal pulmonary embolism. The purpose of the operation is to interrupt the long column of blood in the femoral and popliteal veins the site from which practically all fatal pulmonary emboli arise.

The femoral vein may be interrupted either just distal to the saphenofemoral junction or just distal to the junction of the superficial and deep femoral veins. It should not be interrupted above the saphenofemoral junction, especially in elderly patients, since there may be

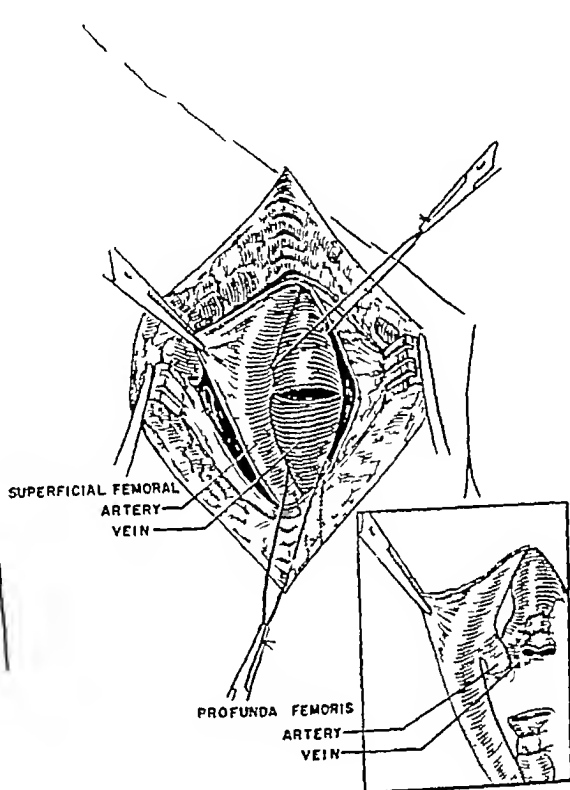


Fig 139—*Interruption of the superficial femoral vein* An operative sketch to show the exposure of the right superficial femoral vein. Note the vertical incision parallel and directly over the femoral vessels, the upper end commencing at the groin crease. The femoral artery is retracted lateralward without completely isolating it. The dilatation in the femoral vein, a constant finding, localizes the site of origin of the profunda femoris vein, as it is always found just proximal to the dilatation. A transverse incision should be used to open the vein, first placing untied ligatures above and below the point the vein is to be opened to control bleeding. The inset shows the divided superficial femoral vein, and both ends doubly ligated with nonabsorbable ligatures. Note that the ligature on the proximal end is so placed that there is no blind segment between it and the origin of the profunda femoris vein (From Linton and Mason and Zintel)

little or no collateral return if this level is chosen. Interruption of the superficial femoral vein (Fig 139) just distal to its junction with the deep femoral may be carried out without danger to the circulation of the extremity in any patient irrespective of his age. In addition, it is

also the safest level for the average general surgeon to interrupt this large venous system, since at this level there are 2 to 3 cm. of vein free of tributaries. Interruption of the common femoral vein (Fig 140), on the other hand, is more difficult since there are a number of branches which arise from it, these may be torn accidentally resulting in hemor

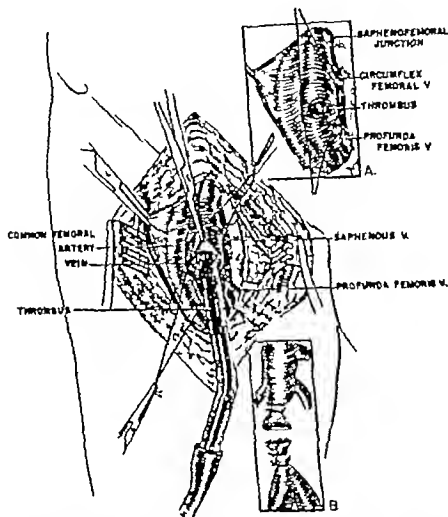


Fig. 140.—Interruption of the common femoral vein and thrombectomy. An operative sketch showing the exposure of the common femoral vein with thrombectomy. The incision is vertical and parallel to the femoral vessels the upper end extending about 2 cm. above the groin crease. Note the tributaries arising from the vein which make it a more difficult interruption than the superficial femoral vein. Thrombectomy of the proximal segment by aspiration using a glass cannula is shown through a transverse incision in the vein with previously placed untied ligatures. The inset shows the vein completely divided with each end doubly ligated proximal to the profunda femoris and distal to the saphenous veins. (From Linton and Mason and Zintel.)

rhage which may be difficult to control, and with danger of damaging the femoral artery which lies in close proximity to the vein. The vein may be tied in continuity, but division of it and ligation of each end with a primary ligature and a secondary stitch ligature distal to it in each stump is considered the better procedure. These ligatures should be of a nonabsorbable type, either cotton or silk. If the superficial

femoral vein is interrupted, this should be carried out at the junction with the deep femoral vein (Fig 139) *A blind segment of superficial femoral vein proximal to the interruption should be avoided, since secondary thrombosis may occur which may be dislodged to produce a pulmonary embolus*

If a thrombus is found in the femoral vein at the time of operation, it is believed a better operation to interrupt the common femoral rather than the superficial femoral vein (Fig 140) This is because another thrombus is likely to develop in the common femoral vein, so that if the interruption is not above the deep femoral vein the clot which may form after removing the primary thrombus may be dislodged by back pressure in the deep femoral system Interruption of the common femoral vein is also considered a better operation in the chronically ill patient, such as the cardiac, who may have to remain in bed for weeks to months Since we have routinely interrupted the common femoral vein in this group of patients, fewer secondary pulmonary emboli have occurred *We believe that the incision used to expose the femoral vein should be a vertical one parallel to the course of the vein rather than a transverse incision* This will permit better exposure of the large blood vessels and also fewer lymphatics will be interrupted The operative incision should be closed with meticulous care to eliminate dead space, and rubber drains should not be used If the patient need not remain in bed for any other reason, he may be allowed up to walk or even sit in a chair within a few hours of the time of operation

There have been few serious sequelae following this operative procedure in our hands There have been two proven instances of death from postinterruption pulmonary embolism in 1000 patients on whom the operation was performed In one the superficial femoral vein was interrupted, and in the other the common femoral vein It was not possible to remove all the thrombus proximal to the femoral vein in the latter patient. If this is the case and the patient has had a pulmonary embolus, interruption of the venous channel should be carried out at a higher level The commonest complication following femoral vein interruption has been a lymph fistula in the groin wound This is not serious, since it usually closes spontaneously within a period of two weeks following the operation There has been no serious instance of infection and only an occasional case of secondary hemorrhage due to slipping of ligatures within a few hours of the operation These of course have necessitated re-exposure and re-ligation of the vessels In a few instances the pain and swelling of the leg secondary to thrombophlebitis may become more severe In these patients marked amelioration of these symptoms can be obtained by a paravertebral procaine injection of the lumbar sympathetic ganglia as recommended by Ochsner

The importance of interrupting the femoral veins as a life-saving procedure is well illustrated by the following case report

Patient Z, aged 54, was referred to us on December 21 1945 because of pain in the left chest and the spitting of blood. Six months previously a diagnosis of coronary heart disease had been made and he was put to bed. Following this he had an episode of right chest pain with hemoptysis. He recovered after several weeks of hospitalization, but two months later he had another attack of hemoptysis. He was taken to the hospital again and a surgeon, finding evidence of deep venous thrombosis in the left leg attempted to interrupt the left femoral vein. Exploration was unsatisfactory because the vein was found to be thrombosed and there was so much reaction around it that an attempt to remove the clot was felt to be unwise. The patient made a fairly satisfactory convalescence following this procedure, but was never well enough to permit his return to his occupation. On December 18, three days before he was admitted to our hospital he again developed chest pain on the left side followed by hemoptysis.

Physical examination showed a well developed and nourished middle-aged man lying in bed complaining of pain in the left chest on deep inspiration. He was

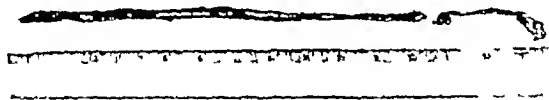


Fig 141 —A photograph of the thrombus removed through the common femoral vein in a patient aged 54. A most careful preoperative examination of the extremities failed to reveal any sign or evidence of deep venous thrombosis. Bilateral femoral vein interruptions were carried out because of repeated nonfatal pulmonary emboli over a period of six months. A rapid and uneventful convalescence followed the venous interruptions.

spitting up small amounts of dark blood. Examination of the lungs was negative except for diminished breath sounds at the left base and a few rales. Abdominal examination was negative. A careful examination of both legs revealed no tender ness, swelling or pain in the calves of the legs on forceful dorsiflexion of the feet. Roentgenographic examination of the chest revealed numerous linear areas of increased density on both sides, which represented the scars of healed infarcts. There was a small amount of fluid in both pleural sinuses. In the posterior gutter on the left there was an area of increased density which had the appearance of a more recent infarct. A diagnosis of venous thrombosis of the lower extremities with pulmonary embolism was made.

On December 22, 1945 one day after his admission to our hospital, the femoral veins of both lower extremities were exposed in the groins. The right femoral vein was found to contain a nonadherent thrombus the upper end extending 2 inches proximal to the deep femoral branch. The common femoral vein was isolated between ligatures. The vein was opened and a clot measuring 15 inches in length was removed from the superficial femoral vein (Fig 141). This clot was untached for the most part so it was very readily extracted with gentle traction. On the left side there was a marked amount of scar tissue around the femoral vein indicating a previous deep thrombosis. The vessel was opened but no thrombus

was found. It was felt that this vein had recanalized since the previous exploration four months prior. The common femoral vein on both sides was doubly ligated and divided.

Following the operation the patient made an uneventful convalescence. The wounds healed kindly. He was discharged from the hospital on his tenth postoperative day. His chest symptoms rapidly cleared, his legs did not become edematous or show any untoward effects following the venous interruptions. He has remained well since the operation, with no other attacks of pulmonary embolism.

Comment—This patient demonstrates the importance of interrupting the femoral veins as a life-saving measure after a patient has had a

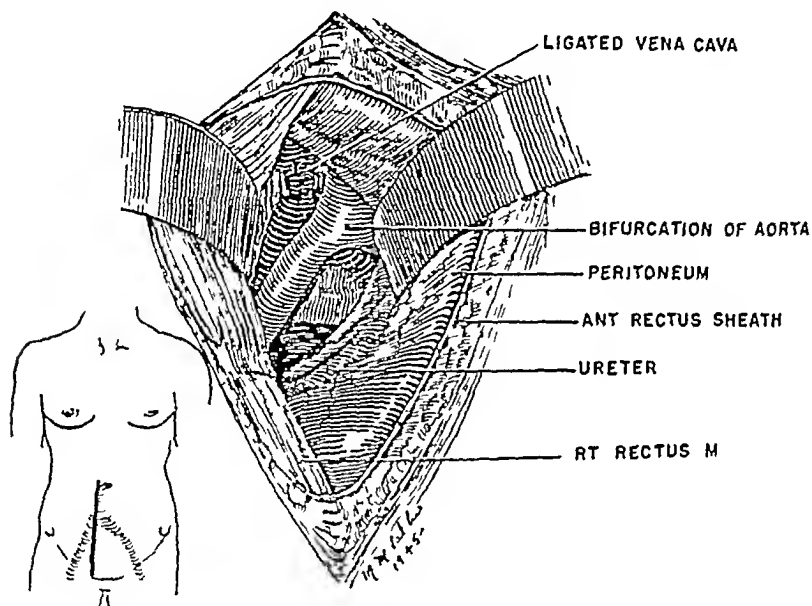


Fig 142—*Interruption of the inferior vena cava.* An operative sketch showing the extraperitoneal exposure of the inferior vena cava. A right paramedian incision is shown retracting the rectus muscle lateralward, the ureter, peritoneum and its contents medialward. The incision should extend several centimeters above the umbilicus. The inferior vena cava because of its large size is interrupted in continuity with two nonabsorbable ligatures. General anesthesia is the method of choice to expose this vessel. (From Linton and Mason and Zintel.)

nonfatal pulmonary embolus, even though no sign of venous thrombosis is present in the legs. The clot which was removed from the right femoral vein in the above case was of sufficient length, if it had become dislodged, to produce sudden death from massive pulmonary embolism. The rapidity with which a patient with this disease can be rehabilitated is also beautifully demonstrated by this case. Whereas he had been chronically ill for six months before his admission to our hospital, the operation of bilateral femoral vein interruption with thrombectomy restored him to health within a few weeks.

Interruption of the venous system at a higher level than the femoral vein is sometimes necessary. In our hands it is reserved for the unusual case of thrombo-embolic disease, in which the femoral veins have been thrombosed for a week or more and pulmonary emboli are still occurring, or in cases of septic pulmonary embolism secondary to a septic process in the pelvis or the lower extremity. The level of this interruption may be either the inferior vena cava or the common iliac veins. It is our opinion that the former is preferable, since the venous systems of both extremities and the pelvis can be interrupted through a single incision. The exposure of the inferior vena cava is best obtained by an extraperitoneal approach either through a right flank or preferably a right paramedian incision, retracting the rectus muscle lateralward. The peritoneum is readily stripped out of the iliac fossa and displaced medialward to expose the bifurcation of the inferior vena cava (Fig. 142). Interruption of this large vessel is carried out by two ligatures of silk or cotton. The vessel is usually ligated in continuity, since it is difficult to free up enough of it to divide it and then ligate each end safely. It should not be interrupted proximal to the renal veins, since death will rapidly ensue if this is done.

SUMMARY AND CONCLUSIONS

1. The majority of deaths from massive pulmonary embolism can be prevented.

2. Bilateral femoral vein interruption is a safe procedure which will prevent massive fatal pulmonary embolism in patients with deep venous thrombosis of the lower extremities.

3. This operation should be carried out (a) on any patient who develops a warning nonfatal pulmonary embolism, irrespective of whether the legs show signs of venous thrombosis, or (b) on any patient who develops evidence of deep venous thrombosis of the lower extremity. Since it is unusual to find all the signs of venous thrombosis present in a given case, the decision to operate may depend on one or two.

4. Bilateral femoral vein interruption should be carried out on all patients with deep venous thrombosis even if the diagnosis is made in only one extremity.

5. Bilateral femoral vein interruption is recommended as a prophylactic measure before or at the time of major abdominal operations for carcinoma in patients over 50 years of age and in those subjected to open reduction of intertrochanteric fractures of the femur.

6. After the first signs of deep venous thrombosis in the lower extremity have been recognized, the operation of bilateral femoral vein interruption should be carried out immediately instead of waiting until the thrombosis has obviously involved the femoral and possibly the iliac veins, because early operative treatment will reduce the post-

operative sequelae and also prevent death from fatal pulmonary embolism

7 The morbidity of thrombo-embolic disease is tremendously reduced by interruption of the femoral veins

8 Interruption of the inferior vena cava distal to the renal veins is the operation of choice in cases of long-standing thrombophlebitis with pulmonary embolism or in cases of septic pulmonary emboli arising from the pelvis or lower extremity

ESSENTIAL HYPERTENSION: PRESENT STATUS OF THE PROBLEM

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It is well for us to review periodically our knowledge of any disease as ubiquitous as essential hypertension and especially to consider recent additions to our knowledge. For, without being aware of it, a gradual change may take place in our thinking about a disease that can have important bearings on our clinical management of it. This is true in the case of hypertension, our concepts of which on first thought might be said to have undergone no major change in the past five years. Although during this period there has been no important advance in specific methods of treatment of the disease, definite alterations have taken place in our ideas of the underlying mechanisms involved and of their relative etiological importance.

NEWER CONCEPTS OF ETIOLOGY

Role of the Kidney—During the war years the role of the kidney in the causation of essential hypertension has received less and less emphasis. While no one denies that renal abnormalities may produce arterial hypertension, it is now agreed by most students of the disease that typical essential hypertension is usually not accompanied early in its course by significant disturbances of renal blood flow or function either bilaterally or unilaterally. Just as it has been shown by statistical methods that gross unilateral renal disease, such as an atrophic or a pyelonephritic kidney, is relatively uncommon in human hypertension so with increasing experience it is becoming apparent that diffuse, hypertensive vascular disease is rarely found in the kidneys prior to or even early after the appearance of hypertension. The renal vascular pathology that appears later is now almost universally recognized to be the result and not the cause of the hypertensive process. Although it may be associated with urinary abnormalities the structural disorder is closely correlated with the functional impairment of the kidneys in any given hypertensive patient. Furthermore the degree of the pathological and physiological disturbances may bear no relationship to the level of the blood pressure. Such considerations further extend our doubts that the Goldblatt mechanism is a frequent cause of human

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essential hypertension, or that "millions of tiny sclerotic clamps" on the renal arterioles precede the elevation of blood pressure. Therefore, although we insist that every severely hypertensive patient have a consideration of the possibility that abnormalities in the renal tract may be responsible, we have learned not to expect to find such an explanation in the vast majority of our cases.

Role of Hereditary, Constitutional and Psychological Factors.—Recently there has been a great deal of interest in the familial tendency of patients with hypertension to pass it on to their offspring. Family histories and statistical studies of large groups of cases leave little doubt that this factor plays an important role in the incidence of the disease. It appears that when both parents have a strong family history of hypertension the children are almost certain to develop it later in life, in fact, will develop it earlier than the average hypertensive patient. Statistics also demonstrate that body build and habitus play a definite predisposing role in the disease, which predominates in the wide, pyknic, and especially overweight, as compared with the long, lean type. Finally, a great deal has been written about the role of familial psychological traits in hypertension. Studies of the psychiatric and emotional histories of hypertensive patients seem to show that by nature they are extraordinarily sensitive and/or that in their family lives they have undergone severe, emotionally traumatic experiences. Some investigators have found the typical hypertensive personality to be one that alternates between powerful aggressive tendencies, and strong passive or dependent wishes, resulting in emotional conflict or tension. Although other studies have failed to reveal a consistent profile or pattern, they do confirm the impression that these patients are frequently involved in severe emotional turmoil in which fear, hatred or hopelessness predominate. No one who interviews hypertensive patients from this angle can fail to be impressed with the irritability and emotionality of these patients as a group. Many patients are aware of this characteristic themselves, and most are quite ready to discuss it, once its possible importance is mentioned.

Role of the Vasomotor System.—The majority of hypertensive patients have a wide range of blood pressure readings from time to time, or under different conditions. In fact, the most striking characteristic of hypertensive patients, besides the elevation, is the instability of their blood pressure. Their tendency to respond to pressor stimuli, such as the cold test, with undue elevations of blood pressure, has been emphasized repeatedly. What has perhaps not been stressed sufficiently is the fact that these patients also tend to have precipitate drops of blood pressure during procedures that have little or no effect on normal individuals. For example, after bed rest alone for a week to ten days the blood pressure of many patients will fall to or toward normal. If treated also by sedation, dehydration or sodium deprivation, it al-

most surely will fall. Starvation is another procedure that may markedly reduce the arterial pressure. In fact, in those areas of Europe where starvation is prevalent, hypertension as a clinical syndrome is practically unknown.

During barbiturate narcosis, or spinal anesthesia, hypertensive patients may not only develop normal levels of blood pressure but actually go into collapse. The same is true during pyrogenic reactions induced by intravenous injections of foreign protein which may cause marked falls in blood pressure in the supine position and a tendency to collapse in the upright position, whether or not the fever is blocked by the use of antipyretics. In normal subjects similar procedures cause no significant change in blood pressure in either the supine or the upright posture. Hypertensive patients likewise seem more susceptible to the depressor effects of thiocyanate and nitrite than normal individuals. Finally, there is little question now that a properly performed surgical sympathectomy will reduce the blood pressure of certain hypertensive patients in the supine posture and cause them to collapse in the upright position, at least early after the operation. Similarly, following a cerebrovascular accident or a myocardial infarction, an occasional hypertensive patient may have a marked lowering of blood pressure, sometimes permanently.

While a review of these blood pressure-reducing procedures reveals almost all of them to be potentially debilitating, intoxicating or actually shocking, it is important to bear in mind that they are more so in hypertensive than in normal people. It is further interesting that when they do lower the pressure of hypertensive patients, they may cause clinical improvement, without evidences of severe deprivation of blood flow to vital areas. These facts indicate that one fundamental abnormality in hypertensive patients is vasomotor instability, and further that hypertension is not necessarily irreversible nor its relief incompatible with life and perhaps health.

NEWER CONCEPTS OF PROGNOSIS

Prognostic Difficulties.—One of the chief changes in the past five years has been the clarification of the prognosis of the disease, resulting from further evaluation of symptoms and signs in larger groups of patients, both untreated and treated by various forms of therapy. While of great help the additional five years are still not enough to allow definite conclusions to be drawn concerning prognosis in individual cases. It seems likely that many years will elapse before we have the final answers to such questions. This is so because of the following considerations:

1 Hypertension is a chronic disease. Although everyone may not agree that it should be called benign, no one can deny that in most

cases it runs a prolonged course, and that the progression of its structural and functional disturbances is slow. Patients with mild, essential hypertension may be followed in the office year after year with no apparent abnormality other than the elevation of blood pressure itself. Even those who are seen for the first time with severe hypertension, complicated by vascular and cardiac disease, may be followed for long periods with very little apparent progression, although no specific therapy is given. It is obvious, therefore, that the evaluation of any treatment must depend upon an accurate appraisal of what the disease might be expected to do without therapy.

2 It is frequently a practical impossibility to determine the previous duration of the disease. This is because of the insidious onset of hypertension which usually is attended by few or no symptoms or signs, and is discovered quite by accident in the course of a physical examination, as for insurance. Since few people have such examinations with any regularity, previous information as to the blood pressure is almost always lacking. Therefore, it is usually impossible to say whether the hypertension has been present for months or years.

3 As pointed out above, there may be great variability in the level of the blood pressure, and in the symptomatic course of the disease in different individuals. It would seem of importance to know whether the blood pressure is almost continually or only rarely increased, especially if one believes that many of the ill effects of hypertension come from the elevation of blood pressure itself. However, since the mere taking of the pressure is a fairly potent pressor stimulus for most hypertensive patients, such information is not easily obtainable by a physician.

Prognostic Criteria—With these difficulties in mind, attempts may be made to predict from statistical evidence the probable course of hypertensive disease in any given patient without specific therapy. It is generally agreed that the following factors are unquestionably important.

1 *The level of the blood pressure* While the patient needs to be told repeatedly that the level of the blood pressure alone is not a sure criterion of the severity of his disease, it certainly constitutes the best single aid in making a prognosis. Statistically, the higher the blood pressure, the worse the prognosis, and this applies both to the systolic and diastolic levels. Thus, levels of over 200 mm of mercury systolic and 120 diastolic carry an increasingly grave prognosis as compared with levels below these figures. The height of the arterial pressure is especially helpful in indicating the danger of cerebrovascular accidents which cause roughly 40 per cent of the total deaths from hypertension. Twice as many patients die of cerebrovascular accident in the group with blood pressures ranging continuously in excess of 200 mm of mercury systolic and 120 diastolic than in the group with blood pressures

ranging continuously below 180 systolic and 110 diastolic. However, in assessing the danger of cerebrovascular accident, one should consider not only the basal or continuous type of blood pressure that the patient may have, but also the peaks to which the blood pressure may rise after pressor stimuli. It seems likely that many accidents occur during such peaks of blood pressure.

2. *Size of the heart* Enlargement of the left ventricle, as determined by clinical, x ray or electrocardiographic evidence, is an important sign of cardiac strain in hypertension, and as it increases carries a graver prognosis especially as concerns the danger of myocardial failure and death in myocardial failure. Since 40 per cent of all hypertensive patients die of cardiac causes and about half of these die in failure, it is important to know that cardiac enlargement is a cardinal sign of myocardial strain and possible failure. Left ventricular enlargement, however, bears no relationship to the incidence of death from myocardial infarction. Angina pectoris of course, as a sign of coronary disease, may be a warning of possible myocardial infarction. Abnormalities in rhythm, especially gallop rhythm or pulsus alternans, have the same grave prognostic significance as in other forms of heart disease. The appearance of an aortic diastolic murmur is an additional evidence of cardiac dilatation which, if present, must be used in evaluating the cardiac status.

3. *Appearance of the retina* Fundoscopic examination constitutes an important clinical adjunct in the prognosis of hypertensive disease, since it affords a clear view of the vascular damage that is taking place. It is helpful not only in understanding the visual disturbances, but also the renal disturbances associated with the vascular disease. The appearance of severe hypertensive retinopathy is well correlated with the incidence of death of hypertensive patients in uremia, which causes less than 10 per cent of the total.

4. *Renal function* As stated above abnormalities of renal function and of the urinary constituents are closely related to the severity of the morphological vascular disease in the kidneys of hypertensive patients. Heavy proteinuria and fixation of specific gravity are two of the most helpful signs of diffuse renal disease prior to nitrogen retention.

5. *Physical and emotional activity* The amount of physical exertion that must be supported by the heart and circulation in addition to the hypertension is perhaps the most important necessary consideration in making a prognosis. It undoubtedly accounts for the fact that while hypertension is almost twice as frequent in women as in men the mortality rate is twice as high in men as in women. It has been observed repeatedly that hypertensive patients who are able to curtail their physical activities have a much better prognosis than those who continue to labor or undertake strenuous exercise. Also it seems likely that those patients who are relatively free from continuous emotional

stram and upheaval have a better prognosis than those who are in a constant state of worry, fear, or irritability

6 *Weight* In a sense this factor is but a subheading of the preceding one, but it needs to be considered separately with hypertensive patients. Excessive weight places an unnecessary load on the heart and circulation from which they never can escape, except by weight reduction. Furthermore, it is well known that obesity predisposes to vascular disease, especially arteriosclerosis. These facts should be emphasized in persuading fat patients to reduce

7 *Progression of the disease* This factor is more important in making a prognosis than all the others, since it makes use of them all to allow an appraisal of the course of the disease in the individual patient. Repeated observations and use of all these criteria will afford the physician a running account of what the hypertension is doing to the patient, and at the same time give him his best impression of what it may be expected to do in the future. Although in an occasional patient the disease may suddenly enter the so-called malignant phase with an acceleration of all of the degenerative processes, in the majority of patients it continues to progress year after year at the same pace as previously. In fact, it may not progress, but in about 25 per cent of the cases it may become stabilized or actually slowly regress.

MODERN TREATMENT OF HYPERTENSION

Psychotherapy.—As mentioned above, irritability, anxiety, fear, resentment, and alternate aggression or dependence are typical emotional attitudes of hypertensive patients. They are sensitive to petty annoyances and especially to personal slights, disagreements or altercations. Self-recrimination for these traits is also commonly indulged in by these patients, who may revolve in a sort of emotional vicious circle, especially when they have been told that emotionality aggravates the blood pressure. For the physician not trained in psychiatry the best treatment for these disturbances seems to be the use of reassurance, sympathy and encouragement. It is remarkable how patients will return to the clinic time after time for this sort of treatment and profess to feel much better after it. Only rarely, however, can any definite lowering of the blood pressure be demonstrated. The same may be said after even more thoroughgoing psychotherapy by trained analysts or psychiatrists. Nevertheless, it seems worth while to spend a great deal of time in listening to the personal troubles and difficulties of these patients, in trying to give them insight into their emotional conflicts, and in reassuring them.

One emotional factor that it is necessary for both the doctor and the patient to face frankly is the patient's fear of his disease and its possible dire consequences. So much has been written in the lay literature about the dangers of hypertension that when it is discovered a patient usually

develops a marked fear response to it. In the physician's discussion it is well to ask the patient frankly whether he is afraid of dying or of being invalided. These are questions that most patients may wish to avoid, but once mentioned, usually discuss freely and with relief. As part of the reassurance of the patient it is well to remind him that hypertension is usually "benign," runs a prolonged course, and is compatible with a relatively comfortable life to an old age. Since many patients with hypertension are practically asymptomatic, it is fair to point out to them that the disease will probably continue to have the slight effects in the future that it has had in the past.

Another aid in psychotherapy is the judicious use of *sedatives and hypnotics*. Strangely, it is usually necessary to urge typical hypertensive patients to take sedatives, and especially hypnotics, which they seem to regard as crutches necessary only for individuals of weak moral fiber. Sedatives are useful mainly in conjunction with the regimen of physical and mental rest discussed below. In spite of their tendency to be addicting or at least habituating, they must be used in hyperactive individuals in order to enable them to get adequate amounts of rest. Of the sedatives, the barbiturates are the most valuable because of their convenience and wide range of action, but they should not be given continuously without alternation with the bromides, chloral hydrate or, for occasional use, paraldehyde. They should be prescribed in amounts adequate to enable the hypertensive patient to get seven to eight hours sleep at night, and to rest lying down, and if possible to sleep for one half to two hours during the day. The aim of this therapy is not directly to lower the blood pressure, but to relieve, symptomatically, the hyperirritability and tension of the patient. It may, incidentally, also lower the blood pressure, but probably does so by relieving the emotional aggravation.

Regulation of Routine.—It reassures the patient to have his doctor take responsibility for the type of life that he leads. Thus he likes to have prescribed amounts of exercise, rest, sleep, diet and other details of the daily routine. Since the patient is usually overanxious on the one hand, but quite determined to have his way on the other, in general it is better to encourage rather than discourage him to engage in activities which require mild physical exertion and afford amusement and recreation. This is especially true of exercise in the open air or attendance at functions and entertainments which enable him to escape his troubles or to assert his ego. Thus, emphasis should be laid on how much the patient can do instead of how little, with only a moderate interspersing of periods of rest.

It should be stressed that the patient must not be an invalid but should live as normal a life as possible. It is well to go through his daily routine even down to the details of diet, which are discussed below. In general, the doctor should belittle any of the petty points on

which the patient tends to lay great emphasis, and stress only the few points that are really of importance. Incidentally, too frequent measurements of the blood pressure or return visits to the doctor are usually not only not indicated, but may be of actual harm to the patient, provided he can be encouraged to go independently on his own way.

Depressor Procedures.—Some of the depressor procedures mentioned already, or modifications of them, have been used in the treatment of hypertensive patients, both medically and surgically. Thus, *bed rest* at home, or better, in a hospital, is a time-honored, and still an almost unsurpassed method of treating hypertensive patients. It acts not only to lower the blood pressure but also to lessen the physical load upon the heart and the circulation. Likewise, by removing the patient from the emotional turmoil of life and placing him in a more infantile environment, it may temporarily alleviate the emotional conflicts and their effects upon the heart, blood pressure and circulation.

Dehydration, with sodium salt restriction, sometimes in conjunction with the administration of ammonium chloride, may be used effectively in many patients to bring down the blood pressure in a dramatic fashion. When there has been a marked accentuation of the blood pressure, with or without encephalopathic episodes, this may be most worth while. As a chronic regimen it is less effective, both because the patients do not tolerate it well, since it is unpalatable and markedly debilitating, and also because it is of benefit only temporarily in keeping the blood pressure down. The same may be said of rice and other severe *diets* which markedly restrict the intake of protein as well as salt, calories and water. Moderate decreases in blood pressure may occur following the use of such diets, but the beneficial effects are by no means as dramatic as those reported after the same regimens in nephritic cases. Furthermore, the typical hypertensive personality is not well suited to such rigorous deprivations, since it is usually irritated by even mild restrictions and especially by continuous or frequently recurring ones. In our clinic we stress only two points as regards diet for hypertensive patients: (1) reduced intake of calories to decrease weight, and (2) an adjunct to the first point, reduced intake of fats, both of the animal and vegetable variety. This is of value not only in reducing the caloric value of food, but, theoretically, also in lowering the blood levels of lipoids, which seem to be important in predisposing to arteriosclerosis.

The use of *thiocyanate* is restricted to those clinics where the blood levels of the drug are routinely determined and followed. It is a toxic substance and can produce severe reactions or death. Its mode of action is poorly understood and its effect in different hypertensive patients is variable. We have not been impressed with its usefulness or safety. Likewise, the *nitrites*, while capable of lowering the blood pressure acutely to the point of collapse in both normal and hypertensive pa-

tients, are less useful in chronically lowering the blood pressure from hypertensive to normal levels without the symptoms of weakness or collapse.

Biological substances and extracts which have been claimed to reduce the blood pressure in hypertensive animals, usually of the Goldblatt type, have not been used clinically, at least in sufficient numbers of cases or over adequate periods of time, to be convincing that the results reported in human beings are more than nonspecific. Until such evidence is forthcoming, it would seem well to leave the trial of such agents in the hands of those qualified to test them experimentally. The same can be said of vitamin A concentrates, quinones and various enzymes. So far well controlled studies of the pharmacological treatment of human hypertension indicate that, with the possible exception of thiocyanate, none of the agents advocated for the disease have any consistently better effect than placebos enthusiastically recommended.

Sympathectomy—Mention will be made of *surgical sympathectomy* only in order to acknowledge its effectiveness in selected patients, especially those under fifty years of age, in whom the disease has not been present in a severe form long enough to cause irreversible cardiac or renal damage. In general, it may be said that young, hyperreactive women whose basal blood pressure does not exceed 200 mm. of mercury systolic or 150 mm. diastolic, and who have a relatively high diastolic as compared with systolic pressure, resulting in a small pulse pressure, do better after surgical sympathectomy. Accessory tests of vasomotor lability, such as the cold pressor and posture pressor tests, and the narcotic (amytal) depressor test, when positive, are additional signs that the patient will have a good result after surgical sympathectomy. Every patient should be followed long enough before operation to ascertain that he has a continuous elevation of blood pressure, and not one that will respond to palliative medical treatment, and that his disease seems to be progressing with moderate rapidity and not remaining static without causing any cardiac, renal or cerebral disturbances. Selected on the basis of such criteria patients may properly be subjected to the formidable two stage operation and may have a striking reduction of blood pressure. When the pressure is reduced there is usually an improvement in the secondary signs of hypertension such as cardiac enlargement, hypertensive retinopathy and, occasionally, renal function.

Sympathectomy should be undertaken only by a surgeon thoroughly experienced with the procedure, and then only after due consultation with the local physician and probably also with a medical consultant. These precautions will decrease the number of unnecessary as well as unbeneficial operations. It is still too early to say with assurance whether or not sympathectomy prolongs the life of patients subjected to it as compared with similarly selected control patients treated med

ically However, there is no question that the selection of patients for surgical sympathectomy results in operating on those in whom the prognosis, as a group, is better than average, anyway Until we know more of the prognosis in such patients, untreated or medically treated, we will be unable to evaluate sympathectomy accurately This may require a ten-year study in one clinic of two parallel groups of hypertensive patients alternately treated by sympathectomy and not so treated From what we know at present it seems better judgment to continue to restrict the procedure to patients selected on the basis of such criteria as those outlined above

Cardiac Therapy.—While this is no different from that given in any kind of cardiac insufficiency and in a sense, therefore, might be regarded as symptomatic management, it is one kind of treatment which may be directed specifically against the pathology of the disease Thus, rest, digitalis and diuretics are just as effective in the treatment of hypertensive heart disease as they are in other types of heart disease In addition, it should be remembered that the symptoms of cardiac insufficiency may progress so slowly that they go unnoticed by the hypertensive patient At first the symptoms are mainly those of mild, left-sided heart failure, including increasing dyspnea on exertion, orthopnea, or, occasionally, paroxysmal nocturnal dyspnea The careful physician will usually anticipate these more marked signs of impending failure by noting signs of cardiac enlargement clinically, or by x-ray or electrocardiogram When there are even mild cardiac symptoms, such as dyspnea on exertion and/or increases in the cardiac size, it is wise to digitalize the patient, using the standard dosage This often results in symptomatic improvement and also seems to delay the onset of frank signs attributable first to left, and then to right ventricular failure If evidences of chronic passive congestion and peripheral edema appear, digitalis certainly should be given up to toxicity, and, in addition, the common diuretics such as ammonium chloride and mercupurin should be used, unless there are evidences of severe renal involvement Decompensated hypertensive patients, as a rule, respond well to such therapy It goes without saying that bed rest is a necessary accompaniment of the treatment

Perhaps it needs to be emphasized that improving the heart function by means of cardiac drugs does not raise the blood pressure, on the contrary, it frequently results in lowering it as compensation recurs Mention may also be made here of the use of tobacco and alcohol by hypertensive patients, especially hypertensive cardinals We usually try to eliminate the use of tobacco, since there is evidence that it constricts the peripheral vessels, especially where there may be arteriosclerotic disease On the contrary, we do not discourage the use of alcohol in moderate amounts for the opposite reason Alcohol may also be helpful in elderly hypertensive patients to reduce worry and fear, and promote

a feeling of well being. Of course, it should not be taken in amounts sufficient to produce physical hyperactivity. Thus in the form of one or two cocktails before dinner with friends, it promotes relaxation and allays apprehension. However patients should be warned of its appetite-stimulating effects and also of its own caloric value.

Symptomatic Treatment.—The remainder of the treatment of the hypertensive patient by medical means consists of the use of the ordinary agents for the symptomatic relief of complaints. Hypertensive headaches are not different from the usual neurotic headaches seen in other apprehensive individuals, with the occasional exception of those related to acute cerebral disturbances. They should be treated by reassurance and the usual analgesics. Likewise, constipation, a symptom familiar to those who care for hypertensive patients, is treated by the milder types of laxatives especially mineral oil. Menopausal symptoms, when they are severe enough to require treatment, may be relieved by the use of estrogens. It is surprising how symptomatic remedies of this sort will help a patient and give him the impression that his blood pressure has subsided, when usually it has changed little or only by amounts attributable to the relief of aggravating emotional influences. Such facts remind us that, in spite of the discouraging lack of specific antihypertensive therapy a great deal can be done by symptomatic management that not only makes hypertensive patients more comfortable and contented, but actually prolongs their lives. Until better therapy is available, this kind of treatment seems eminently worth while.

MEDICAL ASPECTS OF RENAL INSUFFICIENCY IN UROLOGIC PRACTICE

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ONE of the most serious and difficult problems in urologic practice is the management of renal insufficiency. Surgical measures have been employed with considerable success in this field for many years, but it is now apparent that appropriate medical therapy not only enhances the safety of surgery but also contributes directly to the correction of biochemical abnormalities and to the eradication of disease processes. However, the proper use of the many effective therapeutic agents now available depends upon an understanding of renal physiological changes during disease, an accurate appraisal of the clinical situation in each patient, and an appreciation of the limitations of the therapy. This clinic will be devoted to a discussion of these questions.

Normal renal function depends upon the presence of healthy renal tissue, an adequate circulation of blood through the kidney, and unobstructed urinary drainage. These three factors are equally important and mutually interdependent. A serious disturbance of any one of them may lead to renal insufficiency, but concomitant disturbances of the other factors may also contribute in various ways to the total picture. Thus, when the kidney is disabled by urinary obstruction, circulatory changes and cellular damage appear very quickly and increase the disorder of kidney function. Consequently, treatment should not be limited to the primary defect, but should be designed to correct the secondary effects as well.

To be most effective, therapy should have clearly defined objectives determined on the basis of a careful diagnostic analysis. In general terms, these objectives are the improvement of renal blood flow, the removal of obstructive processes, and the restoration of parenchymal tissues to health. Although the correction of circulatory abnormalities and the release of obstruction are often accomplished with ease, renal tissue cannot be restored to normal once complete destruction has occurred. It is true that inflammatory and intoxicating processes may be arrested, but this may not prevent continuing destruction of renal tissue, since healing with scar formation may result in further cellular damage.

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The prognosis of renal insufficiency depends upon the extent of renal parenchymal damage and the therapeutic reversibility of the underlying abnormalities. Since it is well known that renal insufficiency in the course of parenchymal disease where tissue damage is pronounced carries an extremely poor prognosis, physicians have come to regard all instances of renal failure with despair. As a result of this pessimistic viewpoint, there is a tendency to carry out diagnostic and therapeutic procedures reluctantly and unenthusiastically. However, renal insufficiency is always reversible to some extent and, in the cases that confront the urologist, is often completely reversible, since obstructive and circulatory factors predominate in these cases. It is of the first importance that *every* case of renal insufficiency be treated as potentially curable.

Since renal insufficiency results in such a complex derangement of the economy of water, electrolytes and other substances, it is not surprising that the clinical picture is correspondingly complex. At first, biochemical abnormalities may be the only indications of renal inefficiency but, later, as these changes become more marked, the symptom-complex of uremia develops. In the past, emphasis has been laid upon the role of renal retention of nitrogen and catabolites in the causation of uremia. It now appears that dehydration, acidosis, loss of base, and other changes may be equally if not more, important. Indeed, renal insufficiency and even uremia may occur in the absence of azotemia.¹ Therapeutic measures are available for the correction of these chemical defects and should be vigorously applied in each patient after analysis has clearly indicated the nature and extent of pathologic changes. Equally important, however, is treatment directed at removing the causes of renal failure. It is in this direction that the management of urologic uremia is particularly satisfying, since causation here is so frequently amenable to treatment. Consequently accurate determination of pathogenesis is very important.

PATHOGENESIS OF RENAL INSUFFICIENCY IN UROLOGIC PRACTICE

In the experience of most urologists, the commonest cause of renal insufficiency is urinary obstruction. Second in importance is infection in the urinary tract and the kidney and third, disturbed blood flow through the kidneys, as a result either of local lesions or of general cardiovascular alterations. Chief among the latter are the circulatory effects of shock, pain, apprehension and fever. If these factors are of sufficient intensity and duration, renal parenchyma may be permanently damaged.

Urinary Obstruction—Etiology—Blockage of urinary flow may occur at any point along the drainage tract. However obstruction is important as a cause of uremia only when drainage from both kidneys is impeded. Thus, ureteral obstruction may result in complete destruc-

tion of a kidney without clinical or biochemical evidence of renal insufficiency, provided the contralateral organ is normal. Obstruction of the urethra, on the other hand, is almost always followed by the development of demonstrable renal functional impairment.

The causes of obstruction are legion and often unexpected. Solid bodies within the urinary passages, such as concretions, foreign bodies, parasites or new growths, may become impacted in the urethra or give rise to intermittent, ball-valve obstruction at the vesical neck. Lesions in the wall of the urinary tract may block off the lumen. Strictures as a result of inflammatory disease are important in this regard. New growths invading the wall of the ureters, bladder or urethra may project into the lumen or constrict the conduits and cause complete obstruction. Likewise, the enlargement of adjoining structures may result in encroachment upon the drainage tract. The most important causes of obstruction in men are prostatic enlargement and urethral stricture. In women, bladder neck obstruction due to fibrosis and contraction of tissues secondary to inflammation or the trauma of childbirth are commonly seen, and in children, congenital abnormalities are the chief offenders.

Pathological Physiology—Obstructive processes interfere with renal function by raising the pressure opposing the flow of urine. It is easy to see how pressure in the pelvis of the kidney would rise following a block anywhere above the opening of the ureter into the bladder. However, the effect on pelvic pressure of obstruction distal to the bladder is less easy to understand. Since the intramural portion of the ureter, in passing obliquely through the vesical wall, acts as an efficient valve to prevent the regurgitation of urine, and since ureteral peristalsis is very active, regurgitation apparently does not occur and the flow of urine from the ureter into the bladder is not reduced, even when the pressure in the bladder is quite high. Thus, there is no change in urine flow when the pressure in the bladder is raised acutely to 20 mm of mercury.² It therefore seems unlikely that back pressure alone is sufficient to cause the dilatation of the ureter and renal pelvis so frequently found following urethral obstruction. However, the protection afforded by ureteral peristalsis and the ureterovesical valve appears to be lost when obstruction is long maintained. Trabeculation of the bladder then develops and permits regurgitation of urine and retrograde transmission of pressure. When blockage is complete, acute dilatation of the bladder produces the same effect more quickly. Another factor that may occasionally play a role in raising the intraureteral and intrapelvic pressure is spasm at the ureterovesical junction, either as the result of local disease or instrumentation.³

Following the elevation of intrapelvic pressure, the urine becomes more concentrated, urea, salts and other substances are less efficiently excreted, and water is retained. The gradient of pressure along the

tubules probably rises, augmenting water reabsorption by slowing the flow of filtrate through the tubules. Interstitial and intraglomerular pressures increase, and glomerular filtration is reduced. Since most wastes are excreted by glomerular filtration, nitrogen and other substances (such as acid catabolites) accumulate in the blood.

When obstruction is unilateral or develops slowly, marked renal parenchymal damage, as a result of hydronephrosis, may occur before renal insufficiency becomes evident clinically. The sequence of events in the development of hydronephrosis is not clearly understood.^{4, 5} Certainly the force under which the distention of the pelvis and atrophy of the kidney occur must be derived from the glomerular filtration pressure. Later, it appears that interference with peritubular blood flow due to increased interstitial pressure may be important in causing atrophy of the proximal tubular segments.

Urinary Infection—Etiology—Urinary infection is due not only to the presence of infective organisms but also to the lack of resistance in the tissues locally. It seems quite clear that infection seldom occurs in a healthy urinary tract. Stasis of urine, in particular, has been proved to enhance the possibility of bacterial invasion, possibly by giving pathogenic organisms an opportunity to gain a foothold in the urinary tract and to grow there. Stasis may arise from obstructive lesions or conditions that permit pooling. In the latter category are included pregnancy and various abnormalities of the bladder and urethra, such as diverticuli, cystocele or urethrocele. Prolonged periods of enforced bed rest may have a similar effect.⁶ Among the causes of lowered resistance are trauma, systemic disease, and debility. Diabetes mellitus, in particular, appears to increase the incidence of urinary tract infection. Harrison and Bailey⁷ found that 54 per cent of diabetic patients presented evidence of urinary infection in contrast to 8 per cent of an unselected group of nondiabetics. Naturally the coexistence of two or more of these factors, as for example, pregnancy and diabetes mellitus, increases dangerously the possibility of urinary infection.

The bacterial agents involved are usually gram negative bacilli, in particular, *Escherichia coli*, although occasionally streptococci or staphylococci may be present. The proximity of the bowel probably explains the character of the usual infecting agents, but doubt still remains regarding the route by which they enter the urinary tract. In some cases they are undoubtedly introduced from below and occasionally, perhaps, are spread by contiguity. However, there seems to be general agreement that primary infective involvement of the kidney (pyelonephritis) is predominantly hematogenous.⁸

Pathological Physiology—Renal insufficiency during infection occurs as a result of toxic and inflammatory effects on renal parenchymal structure, the development of urinary obstruction, and the appearance of renal circulatory abnormalities. When infection is established in the

kidney, small abscesses may form throughout the organ, the tubules may become choked with purulent exudate and the glomeruli replaced by small spherical abscesses.⁸ Great destruction of renal tissue may follow. In addition, increased interstitial pressure within the kidney as a result of inflammatory edema interferes with the operation of residual normal tissue in the manner already described. All these changes, together with the renal circulatory responses to chills, fever, pain and the like, contribute to the development of uremia by provoking detrimental alterations in renal blood flow. It is surprising not that uremia develops, but that it does not do so more frequently.

Infection elsewhere in the urinary tract is not important in causing uremia unless obstruction develops as a result of inflammatory edema. Thus, infection of the prostate or urethra may occasionally cause sufficient swelling to block the outflow of urine. Usually, however, renal insufficiency develops only after the kidney is involved.

The signs and symptoms of urinary infective disorders vary with the site of involvement. However, certain manifestations are nearly always observed. First, as a rule, the local inflammatory condition invokes a systemic response—chills, fever, leukocytosis and increased erythrocyte sedimentation rate. Frequently, invasion of the blood and sepsis occurs. Local pain is often prominent, perhaps as a result of rapid distention of the renal capsule, ureteral spasm, or distention of the bladder. Dysuria and tenesmus are caused by lower urinary tract inflammation.

Functional Abnormalities of Renal Blood Flow.—An important cause of confusion in the diagnosis of renal insufficiency resides in the fact that the kidney plays an important role in the general circulatory system, an activity which appears to take precedence over its function of maintaining the constancy of plasma composition. Normally, the volume of blood flowing through the kidney amounts to about 25 per cent of the total blood flow through the body each minute. Since this relatively large volume is essential for normal urine formation, any condition that interferes with the systemic circulation might, of itself, be expected to impair renal function. As a matter of fact, however, the kidney appears to respond actively to such a condition, by compensatory changes acting not to keep its own blood flow constant, but to bolster the general circulation, causing further and disproportionate reduction in renal blood flow. Thus, blood is diverted from the kidney, where it is apparently not so vitally needed, to more vital areas, such as the brain and heart. This renal reaction, superimposed upon factors that are already operating to reduce renal function, may very easily lead to uremia. Moreover, under these circumstances it may be difficult to differentiate the effects of functional change from those due to structural alteration. Symptoms referable to the extrarenal disease are added to those produced by functional and structural genitourinary disease and serve to make diagnosis still more difficult.

Shock.—In severe shock, renal vasoconstriction and a marked reduction of renal blood flow results in anuria.⁹ If long sustained, irreversible renal damage causes death in uremia. Indeed, this syndrome has proved to be an important cause of fatalities among battle casualties.¹⁰ It is important to realize that similar renal functional changes occur even when obvious signs of peripheral circulatory collapse are absent. Thus, dehydration, severe secondary anemia, or any condition that may lead to collapse may be associated with a reduction of renal blood flow and glomerular filtration rate. As a result, the kidney fails to carry out its excretory tasks efficiently. Superimposed upon this, partial urinary obstruction or localized infection in the kidney and urinary tract, that alone might cause little alarm, may cause frank uremia.

Fever.—The role that fever may play in this regard is not well recognized. Renal hyperemia, without much change in filtration rate is commonly found during fever or during the action of pyrogenic agents even when fever is absent.¹¹ This alone does not seem of very serious import, except perhaps in acute diffuse glomerulonephritis where marked hematuria may develop. However, the associated systemic circulatory phenomena may be dangerous. Some individuals (in particular those suffering from hypertension or arteriosclerosis) appear to be incapable of adequate compensatory adjustments¹² and as a result may pass into a state of profound shock associated with oliguria and renal insufficiency.

Pain.—Apprehension and pain, by causing vasoconstriction within the kidney or obstructive spasm in the urinary tract, may of themselves cause uremia or may exaggerate the extent of an underlying renal functional impairment. Thus, anuria after trauma or, rarely, after cystoscopic examination, may arise on this basis.¹³ Here renal ischemia and urinary obstruction appear to prevent the formation and flow of urine. Similar factors are certainly operative in renal or ureteral colic.

Congestive Heart Failure.—Disease elsewhere in the body may provoke changes in the kidney. This is particularly true of congestive heart failure. The marked increase in venous pressure leads to engorgement of the kidney and diminished renal blood flow. Glomerular filtration is also reduced and renal water retention occurs due to increased interstitial pressure and perhaps also to overactivity of the pituitary. This situation alone may lead to secondary renal insufficiency and so-called "extrarenal uremia." When renal or urinary tract disease is already present, cardiac decompensation may quickly precipitate uremia.

DIAGNOSIS

The diagnosis of the ultimate cause of urologic uremia is often confusing. Urological disorders may mimic lesions elsewhere in the abdomen or may fail to present clinical clues to their presence. The discovery of uremia at once directs attention to the kidney but it may not

at first be apparent that obstruction and/or infection of the urinary tract is at fault. It must always be borne in mind, however, that these conditions are relatively common and that they may be important secondary factors even when intrinsic renal disease is obviously present. *A thorough investigation of the urinary tract is an essential requirement in the study of any case of renal insufficiency.* Nothing is more regrettable than a failure to correct a reversible condition owing to an inadequate diagnostic study.

History taking is here, as always, the heart of the diagnostic work-up. In most cases, a careful history will disclose pathognomonic data, particularly in regard to such symptomatology as pain (character, localization and radiation), abnormal micturition (frequency, dribbling, "poor stream," dysuria, nocturia, hematuria), mental confusion, weight loss, and malaise (chills, "sweats," fever). A search should be made for evidence of disease elsewhere in the body, such as neoplasms, tuberculosis and other systemic illnesses, that might cause urinary tract disorders and of conditions, such as prolonged immobilization, that predispose to these affections. It is particularly important to unearth significant material in the past history. Thus, the disclosure that urolithiasis has occurred in the past or that urinary infection has complicated the course of a pregnancy may throw light upon what has appeared to be a puzzling problem of diagnosis. Likewise, the family history may provide valuable data since it appears that certain familial disorders may be associated with chronic infection and obstruction of the urinary tract.

The *physical examination* should include a careful evaluation of the status of the cardiovascular, respiratory, gastrointestinal and central nervous systems, in addition to the genitourinary system. The presence of hypertension suggests that there may be cardiac involvement, and that electrocardiographic and roentgenologic studies are indicated. It is absolutely necessary that an accurate appraisal of the status of the body water be made. A search for signs of dehydration, acidosis and incipient collapse is vital to such an appraisal. In the examination of the genito-urinary system, the mechanics of micturition should be observed. The bladder should always be catheterized following complete voluntary evacuation since the volume of residual urine can seldom be determined with satisfactory accuracy by percussion. Even catheterization may be misleading if it is not done with care to place the catheter well within the bladder. A rectal examination is required in every patient. Manual examination of the kidneys may be disappointing since even large organs may escape detection. Moreover, palpatory evidence of the nature of the renal enlargement is often misleading. Tumor masses may feel fluctuant and cysts seem stony hard. In any case, important information may be gained by careful manual examination of the lumbar regions with the purpose of locating renal masses and of detecting

inflammatory and painful lesions that may give rise to muscle spasm and local signs of inflammation.

Laboratory methods must be called upon in the analysis of renal function and the plasma composition. Renal functional impairment is usually, though not always, associated with azotemia. The bicarbonate, chloride, calcium, phosphorus and protein concentrations in the plasma should be determined in the analysis of electrolyte and water balance. The daily volume of urine provides important information regarding water balance, especially when considered in connection with daily determinations of the body weight. However, conclusions regarding the presence and extent of obstruction in the urinary tract cannot be based safely on the volume of flow. We have seen marked obstruction associated with a large urinary output. The appearance of an adequate urine flow after a long period of oliguria must also be interpreted with caution. A striking diuresis following a prolonged oliguria or anuria may appear shortly before death in uremia. This phenomenon may indicate almost complete failure of integrated renal functions with reduction of water reabsorption and a resultant loss of most of the small volume of glomerular filtrate that may be formed under these circumstances.

Although urinalysis should be done at frequent intervals, the results must be interpreted cautiously, since the character of the urine may reveal very little regarding the disease processes at work. Proteinuria may be absent despite advanced renal disease. Cylindruria, also, may be misleading since casts may occur, quite without pathologic significance, in any highly concentrated urine. Pyuria is not a certain indication of urinary tract infection for it may occur during the course of acute and chronic diffuse glomerulonephritis when local infection is not demonstrable. Hematuria, on the other hand, is always of significance, although its origin may not be readily apparent.

Urine cultures must always be taken and repeated at frequent intervals. This procedure may not only prove of value in diagnosis but also in assessing the efficacy of therapy. However, the diagnosis of bacteriuria need not wait upon growth in culture. In most instances bacteria may be found on microscopic examination of the urinary sediment.

Over-all renal function tests are of little practical value in the presence of uremia. Sufficient information is gained from a study of plasma composition and the patient as a whole to assess renal function. The urea clearance and the phenolsulfonephthalein excretion test give little additional information.

Cystoscopic examination and retrograde pyelography are usually necessary. The presence of renal insufficiency does not, of itself, contraindicate instrumentation, although it should be remembered that renal shutdown may be induced in this manner. However, the ability to

examine the entire urinary tract and to determine whether renal involvement is unilateral or bilateral permits early and accurate diagnosis and may be of the greatest importance therapeutically. Moreover, bacteriological study of urine obtained from each kidney may lead to accurate localization of a focus of infection. Certainly the slight risk involved is amply justified.

MANAGEMENT

General Measures.—Certain general therapeutic measures are important not only because they improve the patient's condition and may save his life, but also because they clarify diagnosis by removing clinical features that mask and alter the character of the fundamental pathology. In addition, they improve the results of specific therapy. Thus, Greene and Thompson¹⁴ have found that vigorous and adequate preparation of patients permits the use of transurethral prostatic resection with safety and considerably better results than could be hoped for on the basis of palliative measures and suprapubic cystotomy.

Psychosomatic Therapy.—Usually the physician's first task in handling cases of urologic uremia is the alleviation of apprehension and pain. Even the most phlegmatic individual may be assumed to be somewhat apprehensive regarding an illness in which pain, difficulty in voiding, or overt evidence of serious infection may be prominent. Bed rest, of course, is indicated, but it must be prescribed with caution. Many of these patients are elderly, arteriosclerotic, and peculiarly prone to develop phlebothrombosis. Thoughtless insistence upon complete bed rest may prove detrimental. In many, a few hours of activity each day and permission to use a commode rather than the bed pan may be vitally necessary. Apprehension may be allayed by a sympathetic explanation of the nature of the illness, by gentle handling, and reassurance. In this endeavor, active sedation is often necessary. A wide range of susceptibility to sedatives is characteristic of older patients, consequently, these drugs must be used with care. On the whole, demerol, 50 to 100 mg., appears to be preferable to morphine because there is less depression of respiration, a lower incidence of habituation, and less narcosis. Barbiturates may induce psychotic states or habituation and must be used cautiously. Barbitol and phenobarbital are removed from the body largely by renal excretion. Consequently, renal insufficiency is a contraindication to the use of these drugs since high blood levels resulting from retention may cause intoxication. Pentobarbital (nembutal) 0.1 to 0.2 gm. is preferable because it is largely metabolized by the liver. Likewise, paraldehyde (6 to 8 cc. intramuscularly or 4 to 8 cc. orally) and chloral hydrate (0.5 to 1 gm. by mouth) are useful.

Correction of Dehydration and Acidosis.—Correction of water, acid base, and electrolyte imbalances is always an individual problem.

Rough clinical estimates of the extent of dehydration may be made from the history, the character of mucous membranes, and the extent of thirst. As a general rule, it is well to force fluids by mouth (about 2000 cc.) and by cautious intravenous administration (about 1000 cc.) during the first 24 hours following admission to the hospital in particular among those patients who present overt evidence of dehydration. Events thereafter must guide therapy the object always being one of providing the patient with an intake of fluid sufficient to supply his daily requirements and to make up losses. In following these patients, careful records of the water intake and output are absolutely required for an intelligent grasp of daily changes. Likewise, weight measurements, facilitated by bringing scales to bedside, may prove helpful. Isotonic saline is not always a desirable form of fluid therapy since an excess of chloride ion in terms of the plasma composition, may thus be thrust into the body water. Indeed, on most occasions it is likely that a mixture of equal parts of isotonic saline and 5 per cent glucose in distilled water is preferable. This point may be decided at first by clinical appraisal, later by estimations of plasma chloride concentration and of the carbon dioxide combining power (plasma bicarbonate). These measurements should be made as soon as possible and repeated at frequent intervals in order to maintain a firm control of therapy.

The presence of acidosis requires vigorous treatment. This finding usually denotes dehydration, and it may be remarked that fluid administration, alone, is frequently sufficient to return the carbon dioxide combining power toward normal, particularly in those individuals in whom it is not greatly depressed. When this value falls below 30 volumes per cent, however more vigorous measures appear to be necessary. Under these circumstances there may be retention of acidic ions and loss of basic ions. Clinically, the sole manifestation is hyperpnea, but active therapy often is followed by improvement of the mental state and a feeling of well being that are difficult to explain entirely on the basis of water balance correction. It appears that correction of acid base balance has its own reward, possibly as a result of the reestablishment of normal relationships between intracellular and extracellular water.

Sodium lactate Ringer's solution has proved highly satisfactory as a means of repairing sodium deficiency. Care must be taken of course, to avoid overmedication and the substitution of alkalosis for acidosis. The absence of renal mechanisms of compensation during uremia renders the need for caution in this regard even more pressing. Hence, careful readjustment by administering 200 to 400 cc. of 1 molar sodium lactate solution (Lilly) diluted six times in glucosaline is indicated when the carbon dioxide combining power is below 30 volumes per cent. Dosage thereafter must depend upon clinical response and the observed change in the carbon dioxide combining power. In some indi-

viduals, considerably more alkali must be used, in others, very little in addition. Here, as in all of medicine, individualization is absolutely necessary.

The Problems of Oliguria and Anuria—The absence or marked reduction of urine flow usually invokes in the physician a violent urge to do something. Hence, measures that "open up" the kidney have great vogue. These procedures range from excessive hydration to diathermy over the kidney or even decapsulation. As yet, no trustworthy facts have emerged to justify this activity. In behalf of the more commonly used methods of "opening up" the kidney it is declared that hypertonic glucose may increase glomerular filtration rate. Unfortunately, no evidence derived from studies on man supports this assertion. Indeed, the reverse appears true. On the whole, all efforts to invoke a diuresis seem ill advised,* much better results follow the use of measures designed to correct water and electrolyte imbalances, or circulatory maladjustments, such as shock or congestive heart failure. Vigorous therapy of all complicating conditions is of the utmost importance.

Diet—Dietary measures, designed to improve nutrition and stimulate the appetite, are highly valuable. Anorexia is nearly always a serious problem that must be dealt with energetically lest ground be lost. Unfortunately, certain restrictions necessitated by uremia may result in a highly unpalatable diet that further reduces intake. Protein intake must be reduced in order to lessen the excretory load that protein metabolism imposes upon the kidney and possibly, also, to prevent further renal damage. It is necessary to maintain caloric intake and to increase the vitamin supplement. The latter is particularly important in elderly people, who are often irregular in their dietary habits and whose vitamin stores may be depleted at a time when demand increases. The "rice diet" has been enthusiastically advocated by Kempner¹⁶ as ideally fitted to serve the needs outlined above. However, this diet, consisting as it does of fruit juices and carbohydrates, is unappetizing, and if strictly followed may do more harm than good among those who are finicky. It cannot be recommended until more clear-cut and unequivocal evidence of its value is at hand. Certainly an effort to provide an attractive, tasty and well-served diet is often repaid many-fold in improved health. Moreover, good food has definite psychotherapeutic value in reassuring and encouraging the elderly invalid.

Specific Measures.—In a very real sense, the corrective therapy of acidosis and dehydration is specific. In most cases of urologic uremia,

* The use of diuretics is definitely contraindicated in this situation. Even where congestive heart failure is a contributing factor, agents of this type are not only of little help but may even be dangerous. Once urine flow begins and there is definite diminution of the renal dysfunction, diuretics may be used. However, caution should be used when there is difficulty in secreting a dilute urine (see reference 15).

such measures are merely palliative rather than curative. Fortunately, in these cases additional methods are at hand to combat the underlying causes of renal insufficiency, measures that may often produce complete and satisfactory cures. It is not within the domain of this paper to discuss these specific surgical procedures by which obstruction may be relieved or infection eradicated, but certain medical contributions in this direction may be mentioned.

Chemotherapy—Chemotherapy has scored many gratifying successes in the suppression of urinary infections and may be expected to produce still further advances in this field. The sulfonamides suppress infection by gram positive and certain gram negative organisms. Sulfathiazole is generally considered the drug of choice in this connection because it appears to have fewer undesirable side effects, a wider activity spectrum and greater solubility than most other sulfonamides. An initial dose of 0.5 to 1 gm. is given and the level in the blood and urine sustained by regular doses of 0.5 to 1 gm. three times a day. The other sulfonamides may be used when idiosyncrasy or other ill effects attend the use of sulfathiazole. The antibiotics have not been thoroughly tested but it appears that penicillin has value only in infections by gram positive organisms, in particular the staphylococci and streptococci. Streptomycin has been enthusiastically advocated as a urinary antiseptic, but it is, as yet, too early to evaluate its ultimate position in treatment.

Temporary Drainage—Urethral obstruction may often be relieved immediately by catheterization and the free drainage of urine then followed by improvement in renal function. Apparently the reduction in the intrapelvic pressure by the release of impounded urine permits more efficient excretion of water and urea. In addition irrigation of the bladder at regular intervals by syringe or by an automatic siphoning device, with normal saline or 0.8 per cent sulfanilamide solution, is of value. Irrigation brings local infection quickly under control and aids in preventing subsequent stasis and infection by promoting the restoration of bladder tone. The precise renal functional changes that are associated with the clearing of uremia during temporary drainage are not understood, but it appears that a reduction in renal interstitial pressure leads to improvement of renal blood flow and glomerular filtration rate. In any case, the beneficial effects of these measures may contribute importantly to the success of subsequent surgical procedures.

Obviously uremia on the basis of urologic disease often demands a cooperative effort by urologist and internist. This cooperation has a mutually stimulating effect that results in improved therapy and better results. Here, as in many other areas of medical practice teamwork is of the highest importance.

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PSYCHOGENIC OR "HYPOTHALAMIC" AMENORRHEA

EDWARD C. REIFENSTEIN, JR., M.D., F.A.C.P.*

THE diagnosis of amenorrhea is made by the patient herself, she consults a physician to obtain a diagnosis of the cause of the lack of menstruation and to receive treatment to restore the ovarian function to normal. Until recently the primary disturbance responsible for amenorrhea has been sought either in the anterior pituitary, in the ovaries or in the endometrium. The purpose of this presentation is to call attention to disturbances in the hypothalamus as a common cause for amenorrhea.

The sequence of hormone actions involved in the maintenance of normal cyclical menstruation is complicated, frequently it is not possible from clinical evidence to determine what part of the sequence has been disturbed in a given case of amenorrhea. The development and refinement of methods for determining the urinary excretion of the anterior pituitary follicle-stimulating hormone and for determining the presence or absence of estrogen activity on the endometrium or vaginal mucosa have made it possible to establish with greater certainty the exact disturbance that leads to amenorrhea.

HORMONE PATTERN OF MENSTRUATION IN THE NORMAL WOMAN

Before the disturbances in the mechanism of menstruation can be discussed, it is necessary to review the sequence of events in the normal individual. These may be summarized dogmatically as follows (Reifenstein¹) the anterior pituitary follicle-stimulating hormone causes a follicle of the ovary to develop and if there is a small amount of the anterior pituitary luteinizing hormone present, to develop the estrogenic hormone, alpha estradiol the estradiol inhibits the follicle-stimulating hormone (so that it does not become excessive) and stimulates the production of more luteinizing hormone (and/or luteotrophin) the increased amount of luteinizing hormone induces ovulation and the

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formation of a nonfunctioning corpus luteum, the luteinizing hormone also stimulates the production of 17-ketosteroid precursors by the adrenal cortex (Reifenstein, Forbes, Albright, Donaldson and Carroll²), luteotrophin maintains the corpus luteum for about two weeks, and causes the release from it of the corpus luteum hormone, progesterone. Estradiol causes the endometrium to proliferate and, when progesterone is produced, the endometrium becomes secretory, when the effect of luteotrophin ceases after two weeks, progesterone is no longer produced, the secretory endometrium is no longer maintained, and menstruation occurs. In the normal individual, a small amount of luteinizing hormone is probably produced continuously from the anterior pituitary under the influence of nervous impulses from the hypothalamus, the periodic release of follicle-stimulating hormone from the anterior pituitary may also be brought about by nervous impulses from the hypothalamus. It is to be noted that a trace of the luteinizing hormone seems to be needed with the follicle-stimulating hormone to cause the follicle of the ovary to produce estradiol, and likewise that a trace of follicle-stimulating hormone seems to be needed with the luteinizing hormone to induce ovulation. Furthermore, the production of luteinizing hormone is inhibited by progesterone.

HORMONE PATTERN IN NONHYPOTHALAMIC AMENORRHEAS

Amenorrhea will occur when the anterior pituitary does not produce its hormones, when the ovaries do not produce their hormones, and when the endometrium is absent or fails to respond to the ovarian hormones (the ability of the endometrium to respond may be destroyed by infection, radium treatment or x-radiation). The hormone pattern in each of these situations is characteristic. If the pituitary does not produce *any* of its gonadotrophic hormones, the ovaries will not produce estradiol, the follicle-stimulating hormone excretion in the urine will be below normal, and probably zero, and the endometrium and vaginal mucosa will show an absence of estrogenic effect. If the pituitary produces its hormones but the ovaries do not, the follicle-stimulating hormone excretion in the urine will become excessive because of the lack of estrogen to inhibit it, and again the endometrium and vaginal mucosa will show an absence of estrogenic effect. If both the pituitary and the ovaries produce their hormones normally and the endometrium cannot respond, the follicle-stimulating hormone excretion in the urine will be normal, and the vaginal mucosa will show evidence of adequate estrogenic effect.

MEASUREMENT OF FOLLICLE-STIMULATING HORMONE EXCRETION

The classification of amenorrheas into the types discussed in the preceding paragraph depends upon the measurement of the exact amount of follicle-stimulating hormone in the urine. Until recently it was pos-

sible to determine by laboratory methods only whether the amount of follicle-stimulating hormone was greater than normal or not. It was possible to establish with certainty the diagnosis of only that type of amenorrhea which was due to a primary disturbance in the ovaries (as, for example, in the menopause), where the follicle-stimulating hormone excretion was greater than normal. All that could be said about the other types of amenorrhea was that the excretion of follicle-stimulating hormone was not greater than normal, it was assumed that, in the absence of a defect in the endometrium, the excretion was low in the other amenorrheas due to a primary disturbance in the pituitary gland.

Recently a modification of the test for the follicle-stimulating hormone in the urine has been introduced (Heller and Heller³, Klinefelter Albright and Griswold⁴), which makes it feasible to test not only for increased levels of excretion of the follicle-stimulating hormone but also for normal or decreased levels of excretion. This modification involves a dialyzing procedure which eliminates the substances in urine toxic to the assay animals (mice) so that the hormone can now be concentrated to any desired degree. This test has now been employed for three years in the Ovarian Dysfunction Clinic (Klinefelter, et al.⁴) Regularly menstruating (normal) females usually excrete more than 66 and less than 53 mouse units per twenty four hours. Patients with amenorrhea due to a disturbance primary in the anterior pituitary excrete less than 66 mouse units and often less than 8 mouse units per twenty four hours those with amenorrhea due to a disturbance primary in the ovaries excrete more than 53 mouse units per twenty four hours, and those with a defect in the endometrium, excrete amounts in the normal range

MEASUREMENT OF ESTROGEN PRODUCTION

In conjunction with this test, three measures have been employed to determine whether or not the ovaries are producing estrogen (1) the endometrial biopsy, (2) the vaginal smear, and (3) the occurrence of bleeding following the termination of a short course of progesterone (5 mg. intramuscularly daily for five days) The ability of the endometrium to respond to estrogen has been determined when indicated by the appearance of estrogen withdrawal bleeding following an adequate course of estrogen (for example, 5 mg. of estradiol dipropionate intramuscularly every five days for 8 to 10 injections) Patients with amenorrhea due to disturbances primary in either the pituitary or the ovaries were found to lack estrogen, those with amenorrhea due to a defect in the endometrium were found to produce estrogen as indicated by the vaginal smear, although the endometrium was abnormal or absent on biopsy and no bleeding occurred after a course of estrogen.

HORMONAL PATTERN IN "HYPOTHALAMIC AMENORRHEA"

Study of a series of patients with amenorrhea soon revealed that, in addition to the types mentioned in the preceding four paragraphs, there is another type where, in spite of complete lack of estrogen, the follicle-stimulating hormone excretion in the urine is neither high nor low, but normal (Klinefelter, et al⁴). Endometrial biopsies and vaginal smears revealed atrophic tissues in these patients, and no bleeding followed a course of progesterone, however, the endometrium was capable of responding to estrogen since bleeding followed the withdrawal of an adequate course of this hormone. When the case histories of these patients were reviewed, it was found that many of them had readily detectable psychogenic factors complicating their illness. The group included nurses and students away from home for the first time, debutantes, immigrants, patients with sexual maladjustments, women with fear of pregnancy, some patients with anorexia nervosa in whom the amenorrhea preceded much weight loss, women whose husbands were away in the war, and superstitious patients who developed amenorrhea following a fright. The case histories of two typical patients are given subsequently.

The exact disturbance in this group of patients that leads to amenorrhea is not fully established. There is considerable circumstantial evidence to suggest that the primary difficulty is a loss of the nerve impulses from the hypothalamus so that the pituitary does not release the luteinizing hormone. The discharge of nerve impulses from the hypothalamus is presumed to be blocked by the psychological disturbance. Therefore, this condition is termed "hypothalamic amenorrhea." In the complete absence of the luteinizing hormone, the follicle, although stimulated by the follicle-stimulating hormone, does not produce estrogen. Just why the lack of estrogen in this condition does not lead to an increased production of the follicle-stimulating hormone is not clear. It is possible that in these cases the follicle-stimulating hormone is stimulating the ovary to produce some hormone which itself is non-estrogenic, but which is a precursor (or metabolite) of estrogen with the property of inhibiting the production of the follicle-stimulating hormone.

STEPS IN DIAGNOSING "HYPOTHALAMIC AMENORRHEA"

The steps in establishing the diagnosis of "hypothalamic amenorrhea" are as follows: (1) the history of psychic trauma just preceding the onset of amenorrhea is obtained if possible, (2) the excretion of the follicle-stimulating hormone is tested and found to be normal, thus eliminating amenorrhea due to a disturbance primary in the pituitary gland (where the follicle-stimulating hormone excretion is low), and amenorrhea due to a disturbance primary in the ovaries (where the follicle-stimulating hormone excretion is high), (3) the absence of

estrogenic effect on the pelvic tissues is shown by endometrial biopsy and vaginal smear, and by failure to bleed after an adequate course of progesterone (5 mg. intramuscularly daily for five days), (4) the ability of the endometrium to respond to estrogen withdrawal with bleeding is demonstrated by administering and then withdrawing an adequate course of estrogen (for example, 1 mg. of diethylstilbestrol by mouth daily for forty to fifty days, or 5 mg. of estradiol dipropionate intramuscularly every five days for 8 to 10 injections) If bleeding does not occur a history of exposure of the endometrium to infection, radium or x radiation should be sought, and if obtained, will usually eliminate the diagnosis of "hypothalamic amenorrhea." A moderate decrease in the urinary excretion of 17 ketosteroids is consistent with the diagnosis of "hypothalamic amenorrhea."

TREATMENT OF "HYPOTHALAMIC AMENORRHEA"

The most important point to emphasize in the therapy of this condition is the relatively benign nature of the disturbance in many patients. In some the amenorrhea disappears spontaneously as the stressful situation is eliminated nurses or students home for several months of vacation are soon having regular monthly periods again, the end of the war will bring back not only husbands but catamenia to some women with this disorder. In other patients the psychological disturbance is more deeply rooted and requires intensive psychotherapy by a competent psychiatrist. Reassurance that there is no organic disease will often start these women menstruating for several months until their fears again get the better of them. The same mechanism is probably responsible for the minor disturbances in otherwise regular menstrual cycles that beset many women. The woman who believes that "getting her feet wet while menstruating" will do her harm is very apt to miss her next period. Women skip periods after the death of a dear relative or friend, after narrowly escaping with their lives in automobile accidents, burning buildings bombings or hurricanes or after quarrels involving considerable emotional tension. A simple explanation of the cause of the skipped period by the physician will suffice frequently to restore the cycle to normal. Another group of women with "hypothalamic amenorrhea" have psychological disturbances that are far more difficult to uncover. These are the women who are maladjusted, sometimes on an unconscious level. Psychiatric study and therapy are usually indicated in this group.

Because of the existence of psychological disturbances in many of these patients hormone therapy is rather disappointing. The induction of regular cyclical bleeding by the regular cyclical administration and withdrawal of gonadal hormones may aid the physician in convincing a few of the more suggestible patients that there is nothing organically wrong with them, and may result in the return of normal menstruation.

For this purpose, the administration of 1 mg of diethylstilbestrol by mouth daily for the first three weeks each month is often adequate, the same effect can be obtained by administering the diethylstilbestrol continuously and giving a course of intramuscular injections of 5 mg. of progesterone daily for five days every fourth week

On theoretical grounds the administration of chorionic gonadotrophin regularly or intermittently for several months should result in estrogen production and the return of cyclical menstruation. The experience in the Ovarian Dysfunction Clinic with this therapeutic regimen has not been very satisfactory. Small doses of thyroid hormone (30 mg per day) have had a beneficial effect in a few patients.

A more promising form of hormone therapy in this condition is the continuous administration for a number of months of rather small doses of estrogen (0.1 mg of diethylstilbestrol by mouth daily). There is fairly convincing evidence (Smith⁵) that small doses of estrogen, and in particular of diethylstilbestrol, stimulate the anterior pituitary to produce increased amounts of luteinizing hormone. Two menstrual periods *with cramps* (which usually indicate bleeding from a secretory endometrium, hence, ovulation) followed treatment with small doses of diethylstilbestrol in one of the cases cited here (see Fig 144).

EVIDENCE FOR HYPOTHALAMIC CONTROL OF RELEASE OF LUTEINIZING HORMONE

Some of the evidence that the release of the luteinizing hormone and of luteotrophin from the anterior pituitary is brought about by nervous stimuli coming over the hypothalamic-pituitary nervous pathway has been summarized elsewhere (Klinefelter, et al⁴, Brooks⁶). This includes the observation that cats and rabbits do not ovulate after copulation if the hypothalamic-pituitary nervous pathway is cut, and that mice and rats do not produce functioning corpus lutea except after copulation, this and other evidence (Brooks⁶) suggests that the stimulus arising from coitus causes an impulse to travel down the hypothalamic-pituitary nervous pathway which releases luteinizing hormone and luteotrophin. Furthermore, puberty probably is due to the release of gonadotrophic hormones under the influence of impulses coming over this pathway, with suprasellar cysts interfering with the hypothalamic-pituitary nervous pathway puberty may fail to develop (cf Frohlich's syndrome), with a tumor, infection or other organic lesion in the hypothalamus (Klinefelter, et al⁴) stimuli may be released prematurely and result in true precocious puberty.

Further evidence for an absence of luteinizing hormone in "hypothalamic amenorrhea" is derived from the fact that the urinary excretion of 17-ketosteroids is usually somewhat below normal in these patients. The author and his associates (Reifenstein, et al²) have produced considerable evidence that the luteinizing hormone and/or

luteotrophin stimulates the adrenal cortex to produce the precursors of the urinary 17 ketosteroids. The test for measuring the 17 ketosteroid excretion is described elsewhere (Fraser, Forbes, Albright, Sulkowitch and Reifstein⁷)

EVIDENCE FOR NEED OF LUTEINIZING HORMONE FOR ESTROGEN PRODUCTION

The thesis that the follicle does not produce estrogen unless stimulated by both follicle-stimulating and luteinizing hormones, depends in part on experiments in animals Greep⁸ has shown that pure follicle-stimulating hormone will not produce estrogen except in the presence of small amounts of luteinizing hormone.

Certain experiments in patients with "hypothalamic amenorrhea" lend further support to this thesis. In two patients the lack of estrogen was demonstrated by the failure to bleed following the termination of a course of progesterone. These patients were then given intramuscularly each day for six weeks, chorionic gonadotrophin, a hormone very similar if not identical with luteinizing hormone. After this therapy had been administered for four weeks, another course of progesterone injections was given and following the termination of this, the patients menstruated. One of these experiments is shown in Figure 143. It is suggested that the chorionic gonadotrophin replaced the missing luteinizing hormone and enabled the follicle to produce estrogen.

CASE REPORTS

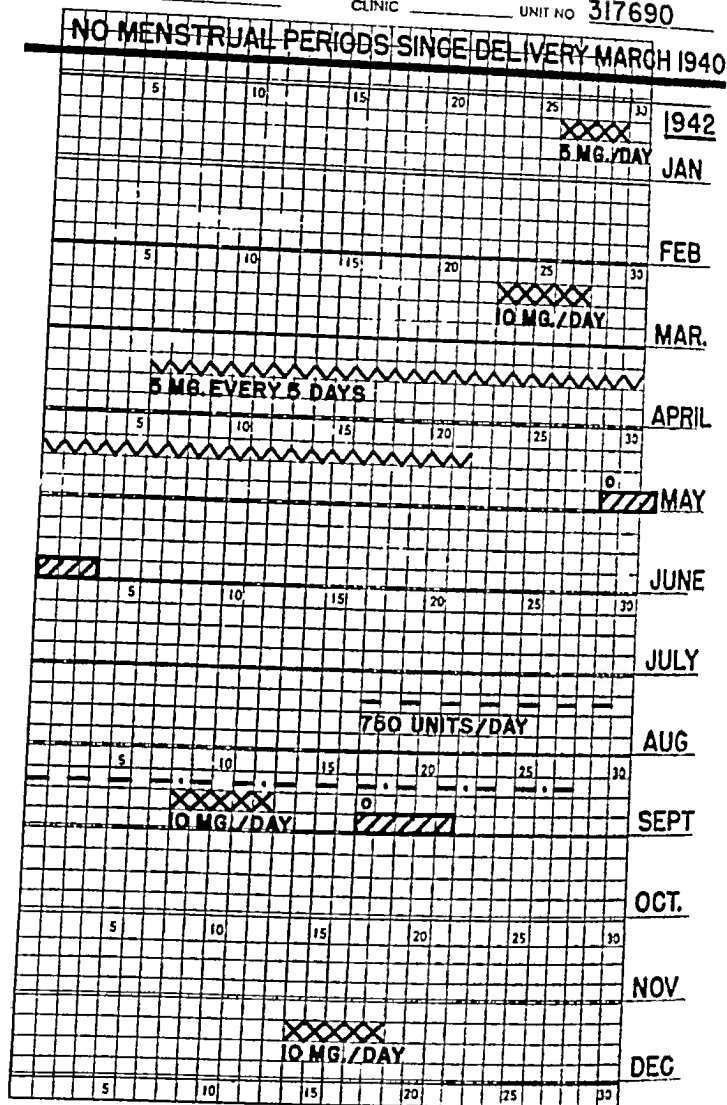
CASE I.—H T (M.G.H. 317690) a married 24 year old housewife, was seen in the Ovarian Dysfunction Clinic in January 1942. Menarche occurred at the age of 14 menstruation was somewhat irregular (every thirty-one to forty two days) and not associated with cramps the patient usually flowed five days. The patient was married in 1938 delivered a normal female child in March, 1940 without particular complication. She was unable to nurse the baby. After that she had no further menstrual periods. She was not weak, had no moulins or "hot flashes," and had not lost weight. The patient was quite positive about not wanting another pregnancy and seemed rather fearful of it she had not experienced orgasm since the delivery. The rest of the history was not unusual. Physically the patient was well developed and well nourished she had adequate axillary and pubic hair—her breasts were small with almost no glandular tissue there was no abnormal pigmentation abdominal examination was not remarkable pelvic examination showed a small introitus a small clean cervix, a uterus that was small, anterior freely movable and not tender the ovaries could not be palpated. The rest of the physical examination was not remarkable.

Laboratory studies revealed that the urinary 17 ketosteroid excretion was 5.4 mg. per twenty four hours and that the urinary follicle-stimulating hormone excretion was positive for 13 but negative for 26 mouse units per twenty-four hours. The patient had no bleeding after a course of injections of progesterone 5 mg. daily for five days (see Fig. 143) she also failed to bleed after a course of injections of progesterone 10 mg. daily for five days (see Fig. 143). However after a series of 10 injections of estradiol dipropionate 5 mg. every five days, she had estrogen-withdrawal bleeding for five days. The patient was then given 750 units

Form 117

NAME: H.T.

CLINIC _____

UNIT NO 317690

PROGESTERONE

ESTRADIOL DIPROPIONATE

MENSTRUATION

NO CRAMPS **CHORIONIC GONADOTROPHIN**

Fig 143—Effect of hormone therapy on menstruation in “hypothalamic amenorrhea” (Case 1) For discussion, see text

of chorionic gonadotrophin daily intramuscularly for forty-three days, twenty three days after the start of this medication, she was given in addition 10 mg of progesterone intramuscularly each day for five days, and following the withdrawal of

this hormone the patient bled for five days while still receiving chorionic gonadotrophin (see Fig 143). During the next two months there were no spontaneous periods; therefore another course was given of progesterone injections 10 mg. intramuscularly each day, and again there was no vaginal bleeding.

Comment—The follicle-stimulating hormone excretion was normal in this patient, in spite of this there was no bleeding after adequate courses of progesterone and the breasts were small, both indicating lack of estrogen production. The uterus was capable of responding to estrogen, as indicated by bleeding after estrogen withdrawal. These findings indicate a diagnosis of "hypothalamic amenorrhea." The 17-ketosteroid excretion was somewhat below the average normal level, a finding which is consistent with this diagnosis. The psychological disturbance is probably related to fear of pregnancy. The demonstration that the administration of chorionic gonadotrophin (which is very similar to luteinizing hormone) resulted in the production of estrogen (as indicated by bleeding after a course of progesterone) is evidence that favors the thesis that the lack of luteinizing hormone is the cause of the lack of estrogen (see discussion elsewhere in this paper).

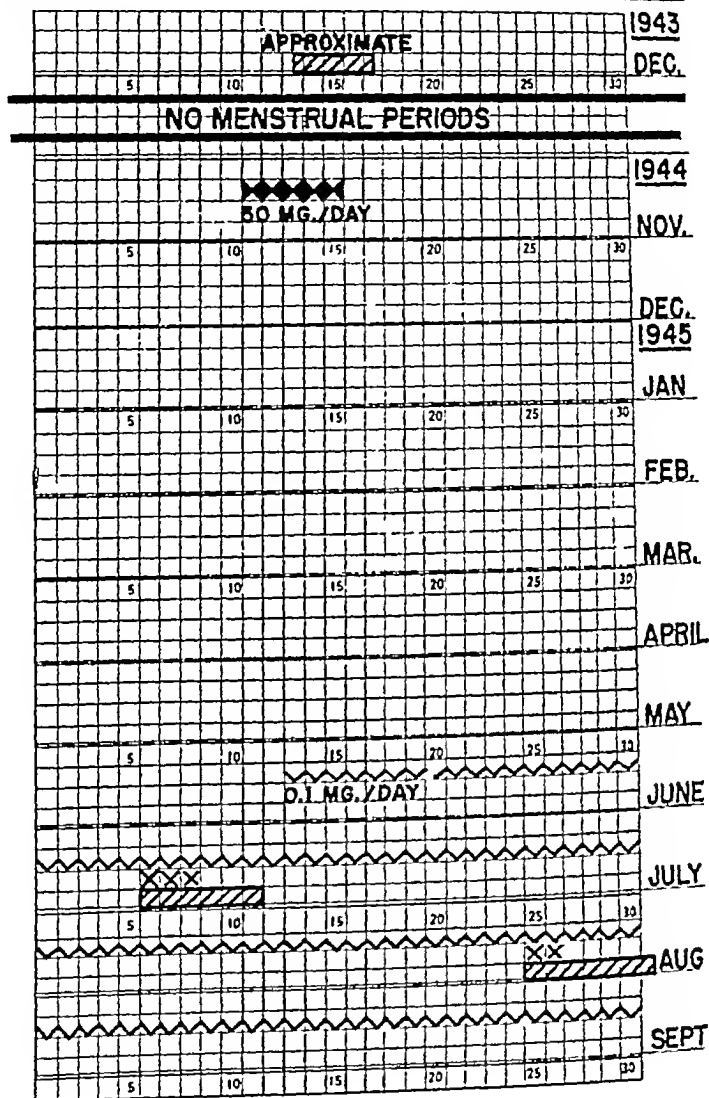
CASE II—L. P. (private patient) a single 25 year old school teacher was studied in July 1944. Menarche occurred at the age of 14; menstruation was always irregular (every two to three months) and only once associated with cramps; the patient usually flowed for three to four days. Menstruation became very irregular two years before study; the last spontaneous period occurred in December 1943. The patient had always been slightly overweight; she was strong and otherwise well, she had experienced no definite "hot flashes" and had not developed hysteria. During childhood the patient had rheumatic fever but at the time of examination she had no evidence of cardiac involvement. From January to June, 1944, she received thyroid medication, amphetamine sulfate, and several courses of estrogen from another physician; there was bleeding following the withdrawal of the estrogen on several occasions. The last medication was taken June 15, 1944. The patient slept with a 15 year old sister. She would not admit any emotional problems but became embarrassed and evasive when questioned about "boy friends." The rest of the history was not remarkable. Physically the patient was well developed but slightly overweight; breasts were rather small, but gland tissue was present, axillary and pubic hair was normal in amount. Abdominal examination was not remarkable; pelvic examination showed a marital introitus, a small smooth cervix, a uterus that was small, anterior, freely movable and not tender; the ovaries could not be palpated. The rest of the physical examination was not remarkable.

Laboratory studies revealed that the urinary 17-ketosteroid excretion was 4.7 mg. per twenty four hours and that the urinary follicle-stimulating hormone excretion was positive for 13 and negative for 28 mouse units per twenty four hours. An endometrial biopsy was attempted July 24, 1944 but the endometrium was found to be atrophic. The patient failed to bleed after 50 mg. of anhydrohydroxyprogesterone by mouth daily for five days (see Fig 144). However subsequently when given a similar course of anhydrohydroxyprogesterone shortly after a course of chorionic gonadotrophin 500 units daily for seventy days, she bled for two days (Fig 144 has been simplified by the omission of this experiment). On June 17, 1945 she began to take diethylstilbestrol 0.1 mg. by mouth daily and con-

Form 122

NAME: **E P.**

CLINIC _____

UNIT NO. **PRIV. PT.**

MENSTRUATION

ANHYDROHYDROXY-PROGESTERONE

DIETHYL STILBESTROL

CRAMPS

Fig 144—Effect of hormone therapy on menstruation in "hypothalamic amenorrhea" (Case II) For discussion, see text.

tinued it without interruption for three months. After twenty-five days of this medication she experienced menstruation for six days *with cramps* and fifty days later another episode of bleeding for seven days *with cramps* (see Fig 144)

Comment—This patient had a normal follicle-stimulating hormone excretion, but lack of estrogen effect on the endometrium as indicated by the atrophy found when biopsy was attempted. The breast development probably resulted from this previous estrogenic therapy. The uterus was capable of responding with bleeding, the administration of chorionic gonadotrophin was followed by estrogen production as indicated by bleeding after the course of anhydrohydroxyprogesterone. In this patient the 17 ketosteroid was low as in Case I. The psychological disturbance was not definitely uncovered.

The most interesting feature of this case is the appearance of two periods with cramps after the administration of very small doses of estrogen. Cramps usually indicate bleeding from a secretory endometrium and are presumptive evidence of ovulation. The patient had had cramps with menstruation only once before in her life. She is being observed further to see whether menstruation with cramps will continue under this therapy.

Subsequent course (July 1946) The same dosage of diethylstilbestrol (0.1 mg. daily by mouth) has been continued without interruption for an additional ten months during which the patient has had four more episodes of menstruation with cramps (November 1945, December 1945, March 1946 and June 1946).

SUMMARY

Attention is called to a syndrome described under the name of "hypothalamic amenorrhea" by Klinefelter, Albright and Griswold¹ in which overt or latent psychological disturbances are thought to prevent the release of luteinizing hormone from the anterior pituitary gland and hence to interfere with the production of estrogen by the ovarian follicle so that the endometrium becomes atrophic and menstruation ceases. The follicle-stimulating hormone excretion by the pituitary is normal in spite of the lack of estrogen, which is interpreted to mean that the follicle produces in the absence of luteinizing hormone a non-estrogenic hormone which inhibits the follicle-stimulating hormone and prevents it from becoming excessive as it does in ovarian failure amenorrhea. The evidence favoring this interpretation, the steps in the diagnosis of this condition, and the implications concerning therapy are discussed. Two cases illustrating this syndrome are presented.

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DIABETIC COMA AND HYPERGLYCEMIC STUPOR COMPARED

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THE admission of an unconscious diabetic boy with urine and blood free from acetone bodies with fever of unexplained origin followed by death and a postmortem demonstration of a large amount of glycogen in the liver, has led us to the use of the term "hyperglycemic stupor with hyperpyrexia." The course of events leading up to the terminal illness of this young man was accurately known and its consideration is instructive in relation to present concepts of the nature of diabetic coma and its proper treatment. The finding of a urine free from diacetic acid and acetone in a patient otherwise apparently suffering from diabetic coma is always disturbing. A second patient is reported here, truly in diabetic coma also without ketonuria, whose recovery with liberal doses of insulin provides a contrast to the first case and also throws light upon the relationship between carbohydrate present in the body fluids during diabetic coma and the character of the treatment needed.

HYPERGLYCEMIC STUPOR WITH HYPERPYREXIA

CASE I (23935) —A boy aged 19 years developed diabetes eighteen months before admission and had received insulin during the intervening months. Treatment had been somewhat haphazard and control of the diabetes inadequate. Three days before admission he broke his insulin syringe. Probably no insulin was taken subsequently.

He entered a hospital at 11:30 A.M. on January 21, 1944, with ketonuria and a blood sugar of 250 mg. per 100 cc. House physician and consultant recorded marked Kussmaul respiration, soft eyeballs, dry tongue and skin, semicomatose state and acetone breath. The temperature was 99.8° F., respiration 32, pulse 88. He was repeatedly incontinent of urine during the afternoon and a catheter was passed twelve hours after admission and 500 cc. of urine obtained. Thirty units of insulin were given on admission and orders were left for 30 units of insulin to be given every two hours if the urine test showed glycosuria. The failure to collect urine resulted in no insulin being given from admission until twelve hours later. He was then given insulin about 30 units every two hours and received a total of 200 units during the second twelve hours. Shortly after admission glucose administration was begun and continued in accordance with Table 1. At the bedside was a pitcher of orange juice with sugar added and the boy was able to take this by mouth for the first eight hours. Thereafter he took nothing by mouth. He received dilaudid, grain $\frac{1}{2}$, soon after admission. In addition to 115 gm. of carbohydrate

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taken by mouth in the form of orange juice sweetened with cane sugar, he received 285 gm of glucose intravenously

The patient was transferred to the New England Deaconess Hospital at 11 30 A.M., January 22, 1944. Under Case 30, Table 4, are given various data including blood sugar 678 mg., blood carbon dioxide 23 volumes per cent, and nonprotein nitrogen 73 mg per 100 cc. The rectal temperature was 104° F., blood pressure 90/70, skin hot, dry and mottled, pulse 130, eyeballs soft, reflexes normal, white blood count 4700 and 5800. The urine contained no blood, 1 to 4 white blood cells, many granular casts, sugar 2 per cent, no acetone or diacetic acid.

Because the patient's neck seemed a little stiff, a lumbar puncture was done which showed an essentially normal spinal fluid, total protein 51.5 mg., chloride 119 m eq., no cells.

With 220 units of insulin given promptly the blood sugar fell to 220 mg and the carbon dioxide rose to 40 volumes per cent. The blood, analyzed by a modified Nanavutty method,¹ contained less than 5 mg of acetone bodies per 100 cc., i.e., too little to be quantitated by the method used. The patient died nine and one-half hours after admission without regaining consciousness.

TABLE 1 (CASE I) —ADMINISTRATION OF GLUCOSE SOLUTION AND SWEETENED ORANGE JUICE

Time	Volume, Cc	Method	Glucose		Insulin, Units
			Per Cent	Grams	
Jan 21, 1944					
Noon	200	I V	5.0	10	30
12-8 P.M.	1000 (orange juice and sugar)	Oral	—	115	0
6 P.M.	1000	Clysis	2.5	25	0
11 P.M.	2000	I V	5.0	100	0
11 P.M.	4000	Clysis	2.5	100	30
Jan 22, 8 A.M.	1000	I V	5.0	50	170 (during night)

A summary of the postmortem examination follows. Clinical diabetes mellitus with acidosis, pulmonary congestion and edema, petechiae, left ventricular and left auricular epicardium, fatty change in liver, congestion of spleen and kidneys, atherosclerosis, aorta. Liver Capsule negative. There is an extensive vacuolation of liver cells which appears in two different forms. Markedly predominant is a vacuolation most pronounced in the periportal areas. In this type the edges of the vacuoles are ragged and the spaces contain small amounts of fine granular material. In contrast are the less pronounced well-defined refractile vacuoles. Appropriate stains show the former to be glycogen vacuoles and the latter fat vacuoles. The liver is otherwise well preserved. Immediate cause of death in this case was undetermined. Signed—Shields Warren, M.D.

Comment—The boy evidently entered the first hospital in rather early diabetic coma. Acidosis was not far advanced as was evidenced by the fact that he could take orange juice by mouth during the first eight hours and did actually take 1000 cc. that way. Hyperglycemia

must steadily have increased. Actually when, after a delay of ten hours, he finally received a total of 200 units of insulin, ketosis was abolished so that when he was transferred to the New England Deaconess Hospital no ketone bodies were demonstrable in either the blood or the urine. The effects of excessive administration of glucose and inadequate insulin dosage were shown in the blood sugar of 678 mg., the persistent reduction in the blood carbon dioxide, the elevation of the blood nitrogen and the fever. It must be remembered that 8000 cc. of fluid were given by needle only after six and one-half hours of intensive administration of orange juice and sugar by mouth. Actually the situation may be compared with the condition produced in the laboratory by Himwich² in animals made diabetic by pancreatectomy. In such animals if hyperglycemia is allowed to increase by omission of insulin and if none or insufficient liquid is given, the animals develop intense dehydration and fever. Indeed, this dehydration and fever may be fatal. In our case the effects of this intense accentuation of hyperglycemia and dehydration during the first six and one-half hours of treatment seem to have produced irreversible changes in the brain with unconsciousness from which recovery was impossible. Again comparison may be made with cases of irreversible or hyperglycemic insulin coma with occasional fatal results reported by Wortis and Lambert.³ These patients were given insulin hypoglycemia for mental disease and when they received intravenous glucose to bring about recovery from hypoglycemic shock, in certain cases hyperglycemia and fever occurred with protracted coma, permanent cerebral damage and even death. Himwich explains the hyperpyrexia as due to so great a loss of fluid that blood cannot be spared for the periphery and for that reason the heat loss of the body becomes inadequate.

A striking finding at autopsy in Case I was the large amount of glycogen in the liver cells. When these cells were stained, the appearance of the glycogen resembled that shown in the liver cells of dogs reported by Astwood and associates.⁴ In their dogs constant intravenous infusion of glucose was given and the dogs died at the end of seventy hours. The glycogen content of the livers reached 19 per cent in one dog and in all dogs the liver cells were filled with glycogen. The dogs died of liver failure with jaundice, reduction in prothrombin time, loss of blood protein and anuria. Those dogs were not diabetic, but a vulnerable diabetic patient might easily die in an early stage of liver failure after a much shorter period of overfeeding with glucose.

The development of fever seems to occur when the administration of glucose is rapid and excessive. Thus Astwood's dogs given glucose solution in such excessive amounts (2.5 to 3 gm. per kilogram per hour) that death occurred inside twenty-four hours, developed fever but dogs who received glucose at slower rates and lived for periods of three to ten days did not have fever. In diabetic coma the decline in rectal

temperature to levels of 94° to 96° F is associated with both ketonemia and great loss of base. It seems likely that the rapid return to normal temperature in the case of coma is due to restoration of base in tissues rather than to relief of ketonemia.

Conclusion—In an early case of diabetic coma, progression to the stage of unconsciousness may follow the administration of carbohydrate without sufficient insulin. If then insulin is given, ketosis may be abolished but hyperglycemic stupor with hyperpyrexia may persist and death may result.

DIABETIC COMA WITH KETONEMIA BUT NO DIACETIC ACID IN THE URINE

CASE II (25957)—A woman, aged 56 years, entered the Deaconess Hospital January 19, 1946, at 8 P.M. She had left her home early in the morning propped up in an auto but because of delay on the road she had arrived later than expected and was then entirely unconscious. Diabetes probably began in July 1944 with polyuria, but was not diagnosed until about January 16 when glycosuria was found.

Upon admission the patient was profoundly comatose, but did feebly resist gastric lavage. After recovery, she had no recollection of events from January 19 to 22. Blood pressure was 100 mm of mercury systolic and 80 mm diastolic, the eyeballs were soft, the skin of the extremities dry and cold. The urine showed 4.2 per cent sugar, no diacetic acid, the sediment showed many casts of the typical coma character. As seen in Table 2 the blood sugar was 900 mg. with the carbon dioxide content of the blood 20 volumes per cent and nonprotein nitrogen 63 mg. The blood acetone value was 70 mg. The patient received 500 units of insulin between 5:45 and 9:00 P.M., with the result that the blood sugar fell to 211 mg. at 2:00 A.M. and 69 mg. at 6:30 A.M. the following day. However, she remained unconscious until the morning of January 22.

During the period from January 20 to 22 when she was unconscious, oscillation of the blood sugar was marked because of necessary feeding by intravenous administration of glucose in saline. From 42 to 88 units of insulin per day were given and the blood sugar values ranged between 74 and 420 mg. The acetone bodies disappeared from the blood by early morning of January 20.

The blood carbon dioxide rose to 52 volumes per cent at 10:00 A.M. on January 20.

The prothrombin time was 87 per cent, blood bilirubin was 0.4 mg., icteric index was 9. The following lists tests of bromsulfalein excretion. January 20, 175 mg of dye was injected but none was recovered at the end of thirty minutes. On January 21, 400 mg of dye, 5 mg per body weight, was given and at the end of forty-five minutes 11 per cent of the dye was retained. On January 23, 400 mg was injected and the readings were: ten minutes—74 per cent, twenty minutes—19 per cent, forty-five minutes—17 per cent retention. On January 26, 400 mg. was given and the readings were: ten minutes—59 per cent, thirty minutes—12 per cent, forty-five minutes—5 per cent. Apparent improvement in function was shown by these tests.

As an evidence of the amount of glucose in body fluids during coma the spinal fluid was analyzed a few hours after the patient's admission and after receiving 300 units of insulin. The fluid contained 680 mg of glucose and a blood sugar analysis at the same time showed 624 mg per 100 cc. Many determinations simultaneously of the glucose in venous blood and the cerebrospinal fluid of diabetics have shown that (1) when the blood sugar range is from 80 to 200 mg the glu-

TABLE 2 (CASE II) —DIABETIC COMA

Date, 1915	Hour	Blood			Treatment		
		Sugar Mg	NPN Mg	CO ₂ Vol %	Insulin Units	Normal Saline, LV Cc.	Glucose 5% in Saline LV Cc
Jan 19	6-7 P.M. 0-10 P.M.	960 624	63	20 27	300 200	2000 1000	
Jan 20	2 A.M. 6 A.M.	211 69		52	42		1000
Jan 21	6 P.M. 2 P.M.	133 310			88		1000
Jan 30	7 P.M. 7 A.M. 11 A.M.	74 107 118			56		Diet-carb 159 gm., prot. 65 gm., fat. 79 gm. Discharged recovered.

case of the cerebrospinal fluid is lower by 10 to 80 mg, (2) when the blood sugar is at high levels, as in acidosis, the difference may be proportionately much less, and (3) under the influence of insulin in considerable doses, the decline in glucose concentration in the cerebrospinal fluid may be much less rapid than in the blood

In Table 3, comparisons of blood sugar with simultaneous sugar levels in pleural fluid and cerebrospinal fluid leave no doubt that concentration of glucose in extracellular fluids is approximately the same as that of the blood in diabetic patients

The persistence of total unconsciousness for sixty hours indicated that the damage done to the patient's central nervous system had been severe but was not irreversible. The absence of acetone bodies in the urine could be explained by failure in excretion but the low level of acetone bodies in the blood was not consistent with failing renal function alone. It suggested that as diabetic ketosis had

TABLE 3—CONCENTRATION OF GLUCOSE DETERMINED SIMULTANEOUSLY IN BLOOD AND OTHER FLUIDS IN DIABETICS

Case No	Blood, Mg	Spinal Fluid, Mg	Pleural Effusion, Mg
25957	624	680	
12695	65		68
12695	233		323
26384 3/13/54	303		299
26384 3/14/45	235		308
26384 3/22/45	82		
23910 12/25/46	328	317	

advanced, a stage had been reached in which production of ketone bodies by the liver had ceased. In other patients, unconsciousness has usually occurred only when the concentration of acetone bodies in the blood has been between 100 and 175 mg. Early failure of liver function due to dehydration and acidosis may have explained the low value for acetone bodies in the blood, which finds some support in a series of liver function tests by means of bromsulfalein as given above.

Comment—Ketonemia—In diabetic ketosis diacetic acid, beta-hydroxybutyric acid and acetone, readily formed from the first two, are found in blood and urine and may be discussed as total acetone bodies. In Table 4 are summarized determinations of the total acetone bodies in the blood of patients with diabetes and ketosis with and without antecedent treatment with insulin together with certain other data. It is our practice generally not to include for discussion and comparison of methods of treatment patients with diabetic ketosis in whom the acidosis had not reached a sufficiently advanced stage to produce a reduction of the carbon dioxide content of the blood to 20 volumes per cent (9 millimols) or less. For the purpose of this discussion, however, we have included all cases in which analyses have been done because of ketonuria or prior treatment of ketosis, even where the carbon

dioxide levels in the blood were between 20 and 76 volumes per cent. In Case 2 the blood sugar was 115 mg. and the carbon dioxide of the blood was 55 volumes per cent because the patient, a young woman with diabetes of eighteen years standing, had received 100 units of insulin during the hours immediately preceding her admission to the hospital. The result was a rapid fall in blood sugar without an equally rapid decline in the acetone bodies of the blood. She, therefore, required only 72 additional units of insulin during the next twenty four hours.

In Case 23, a young man with diabetes of twenty seven years duration, the value of 72 mg. of acetone in the blood with a blood carbon dioxide of 76 volumes per cent represents alkalosis resulting from administration of alkali and amphogel in large amounts before admission. The ketosis was still present in moderate degree. The other cases in which the carbon dioxide of the blood varied between 21 and 35 volumes per cent were less advanced instances of ketosis. Without determinations of the carbon dioxide content of the blood as a measure of acidosis, highly erroneous interpretations of the ketonuria or lack of ketonuria would have been made.

In Case 30 of the table, already described (Case I), the patient had received 200 units of insulin during the twelve hours preceding his admission an amount sufficient to cause disappearance of ketosis but not to compensate for the extraordinary intake of glucose and the effect of dehydration and earlier ketosis.

The mental state of the patients in Table 4 is described as unconscious (Unc) meaning that the patient was unresponsive to ordinary painful stimuli drowsy (D) with Kussmaul respiration, responsive to questions but so far from normal that after recovery the patient had no recollection of the events during the period of acidosis or conscious (Con) meaning that in spite of Kussmaul respiration the patient answered questions alertly and later on remembered the events. Of the eight patients who were unconscious only one (Case 30) had a carbon dioxide content of the blood above 20 volumes per cent and he had received 200 units of insulin prior to admission. In this group four patients were unconscious, with acetone values from 65 to 84 mg., three had values from 113 to 167 mg.

The insulin requirement was highest in the patients with the highest degree of acetonemia as indicated by the fact that all patients with blood sugars over 700 mg. had acetone values of more than 75 mg. However the blood sugar values need individual interpretation since in many instances considerable doses of insulin had been given prior to admission.

More important still is the degree of dehydration, shock, and the presence of complications in determining the severity of the state. The insulin requirement exceeded 500 units in the first twenty four hours

TABLE 1--TOTAL ACETONE BODIES IN BLOOD IN DIABETIC ACIDOSIS AND COMA IN THIRTY PATIENTS
(January 1, 1944 to January 1, 1946)

Case No	Mental State	Blood			Insulin First 24 Hrs Treatment	Age, Yrs	Sex	Duration of Diabetes, Yrs	Hospital Case No
		Acetone, Mg Per 100 Cc	CO ₂ , Vol Per Cent	Sugar, Mg					
1	Unc	167	11	1176	550	27	M	13	11256
2	Unc	153	20	564	274	21	F	18	7191
3	D	149	11	750	345	62	F	6	23038
4	D	128	12	721	428	49	F	9	27548
5	D	120	5	875	210	39	F	5	19290
6	Con	118	22	598	162	58	F	12	13388
7	Unc	113	11	735	198	17	M	11	18764
8	D	111	15	366	218	19	F	10	13870
9	D	109	11	328	300	21	M	4	23910
10	D	102	9	482	340	23	F	12	22920
11	D	99	55	115	72	24	F	18	13977
12	D	97	28	342	88	13	F	9	15223
13	D	97	10	606	250	21	F	12	11467
14	D	95	17	920	268	28	F	13	11032
15	D	93	9	1380	1038	63	F	18	10600
16	Con	84	21	375	114	27	M	2	23509
17	Unc	84	13	412	148	19	F	3	20751
18	D	84	13	616	106	17	F	3	20727
19	D	79	12	227	202	16	M	4	26623
20	Unc	76	20	960	512	56	F	1	25957
21	D	75	31	290	84	24	F	7	17779
22	Con	71	30	431	188	17	F	8	23038

23	D	72	70	200	84	33	M	27	5322
24	Unc	70	18	541	332	13	M	7	24289
25	Unc	65	17	616	412	58	M	23	26128
26	D	56	20	408	138	25	F	10	19893
27	Con	51	32	530	66	10	M	2	27247
28	Con	46	35	326	76	52	F	7	17855
29	D	40	27	634	252	68	F	23	3907
30	Unc	0	23	678	220	19	M	2	23935

Unc—unconscious D—drowsy Con—conscious

* Spinal fluid acetone bodies 153 mg Spinal fluid sugar 317 mg

in only three patients whose acetone values varied from 76 to 167 mg. In general, the higher the blood sugar, the more severe the acidosis and the larger the insulin requirement. (Allowance should be made for insulin given at home during the few hours preceding admission in the patients requiring less than 100 units in the first twenty-four hours in the hospital.)

The causative factors in various states of ketosis are grouped by Soskin and Levine⁵ under three headings: (1) disturbance of carbohydrate intake including starvation, high fat diet and vomiting, (2) impairment of liver function, and (3) endocrine disorders including acromegaly, hyperthyroidism, pregnancy and diabetes mellitus.

In nondiabetic subjects, fasting or a diet free from carbohydrate and consisting of protein and fat can lead to a moderate degree of ketosis. Indeed, such a regimen has long been known to produce starvation glycosuria. By this event is meant a condition in which the body will respond to the administration of glucose or other carbohydrate food by glycosuria and a temporary elevation of blood sugar. The condition is a temporary one and should not be compared with clinical diabetes which is characterized by its permanence, the chronicity of hyperglycemia, and other well known sequelae. Peters⁶ has reviewed the literature dealing with this disturbance in the response to glucose following starvation or a carbohydrate-free diet. Actually the production of clinical diabetes by starvation either in animals or human beings is not recorded in his report. The striking facts about the acidosis and the fall in respiratory quotients produced in normal subjects by a diet free from carbohydrate is its temporary character. Thus Higgins, Peabody and Fitz⁷ on such a diet were able to produce a decline in respiratory quotient to 0.69 and an excretion in twenty-four hours of 20 gm of beta-oxybutyric acid in the urine, but within twenty-four hours after the resumption of normal carbohydrate feeding these abnormalities ceased. Root and Carpenter⁸ placed two normal medical students on diets for several days at three levels of carbohydrate intake, namely 350, 75 and 0 to 11 gm per day. The respiratory exchange was measured on alternate days, and for three hours after the ingestion of 50 gm of glucose. One might expect that with such a lowering of carbohydrate intake with undiminished physical activity the need for deposition of glycogen would be so great that all the glucose would be deposited as glycogen and none burned. Actually, acetonuria appeared only in traces in one subject, and no hyperglycemia occurred. The basal combustion of carbohydrate was lowered on the lower diets. The increases in combustion of carbohydrate after ingestion of glucose was lowered also, but less than was expected.⁸

Serious ketosis leading to coma is practically unknown except in diabetes mellitus. Whether the precipitating factor is the omission of insulin, dietary excesses, or increased metabolism as in fever of hyper-

thyroidism the essential feature of diabetic coma is deficiency of insulin, relative or absolute. In the early stage, hyperglycemia, glycosuria and polyuria result from decreasing oxidation of carbohydrate and increasing breakdown of glycogen stores in liver and muscle.

The place of liver function in diabetic coma is admittedly an important one. The deficiency of insulin results in increased glycogenolysis, glycogen deposits in the liver as well as in the muscles are reduced and glucose gives way to fat as a substrate for oxidation in the liver. The result is great increase in ketone body formation in the liver which exceeds the power of the muscles and other tissues to oxidize. The result is accumulation of ketones in the blood and extracellular fluid of the body. The hyperglycemia of diabetic coma results in polyuria and the excretion of ketone bodies removes base. Acidosis and dehydration are in themselves effective in reducing liver function as measured by bromsulphalein excretion. It is well known that as liver function falls in the presence of liver disease, the response of the liver to ketogenic agents such as anterior pituitary extract is diminished. So in Case II, unconsciousness was associated with a blood ketone value of only 70 volumes per cent whereas most diabetic patients unconscious in diabetic coma have blood ketone values from 100 to 200 mg. This itself suggests that failure in liver function so far as production of ketone bodies is concerned had begun. It seems reasonable to suppose that this failure of liver function may explain other cases of far advanced diabetic acidosis in which ketone bodies in the urine are absent and at lower levels in the blood than expected.

In the treatment of such a patient no glucose is needed by mouth or parenterally during the first six to twelve hours, that is, until sufficient insulin has been given to utilize the excess of glucose present. A primary consideration is the amount of carbohydrate available in the tissues of such a patient in coma. An estimation of the amount in the patient under discussion as compared with that in a normal woman is shown in Table 5.

The estimation of the great excess of glucose present in the blood and extracellular fluids of the body should also consider the possible concentration of glucose within the tissue cells. Trimble and Carey⁶ show that in diabetic patients where the blood sugar might range from the neighborhood of 300 mg. without acidosis that a great increase in the sugar of the skin and also, but in a lesser amount, in the muscles occurs. It seems likely that the concentration of glucose in the water phase of the cells under conditions of acidosis and extreme hyperglycemia would increase and probably parallel that of the blood. If indeed, the water phase of the tissue cells was assumed to contain a roughly comparable concentration of glucose as is observed from analyses of blood, then the total glucose in tissue cells and intercellular fluid during coma when the blood sugar is in the neighborhood of

1000 mg would greatly exceed the 210 gm estimated in Table 5. The administration of more glucose at that time is without logical reason until a sufficient amount of insulin has been given, first, to utilize the excess glucose present and, second, to provide a reserve of insulin to make possible the addition of food including protein as well as carbohydrate.

Measurement of the metabolism of this particular patient in diabetic coma indicates total calories of approximately 75 per hour. Since no ketone bodies were eliminated in the urine, and since the blood ketone value became normal in eight hours, it is possible to estimate the calories derived from the oxidation of ketone bodies on the assumption that not long after the administration of 500 units of insulin, excessive ketone production was halted. It is granted we have no clear proof

TABLE 5 —THE AVAILABLE SUPPLY OF CARBOHYDRATE IN THE BLOOD AND EXTRACELLULAR FLUID DURING COMA*

(Woman, 73 kg, liver 1800 gm, muscles 25 kg, 21 liters blood and extracellular fluid, blood sugar 960 mg, total blood acetone bodies 76 mg per 100 cc)

	Diabetic Coma, Gm	Normal, Gm
Liver glycogen	18 (1.0%)	108 (6.0%)
Muscle glycogen	75 (0.3%)	150 (0.8%)
Blood and extracellular fluid (glucose)	210 (0.96%)	17 (0.08%)
Skin (glucose)	24	4
Total grams of carbohydrate	327	279

* Root, H. F. and Carpenter, T. M. Effect of Glucose Administration in Diabetic Acidosis. *Am. J. M. Sc.*, 206:239, 1943.

that excessive ketone production came to an end at any specified time. However, an estimation of the concentration of ketone bodies in an extracellular fluid of similar concentration to the blood, such as the spinal fluid, permits a calculation of the calories derived from the oxidation of the total ketone bodies present when the patient entered the hospital. These amounted to approximately 10 calories per hour as a minimum, with the possibility that in the first few hours of treatment 25 calories of the total 75 per hour might have come from the oxidation of ketone bodies. From observed respiratory quotients during coma, fat combustion might provide from 35 to 45 calories per hour and protein metabolism, calculated from the nitrogen excretion, 12 calories per hour. Actually, if fat metabolism were kept below a rate of 2.5 gm per kilogram of body weight, one factor in controlling ketosis would be controlled according to status hypothesis. It follows from these cal-

culations that actually in coma the oxidation of as little as 2 to 5 gm of carbohydrate would reduce the part in the metabolic mixture played by fat to a safer level. When one realizes that a normal individual, given glucose by vein while at rest, only oxidizes 10 gm per hour, it is reasonable to assume that in diabetic coma in the first few hours one need not aim at oxidation of carbohydrate at any higher rate.

DIAGNOSIS AND TREATMENT OF DIABETIC COMA

Diagnosis.—The importance of early diagnosis in diabetic acidosis cannot be exaggerated. The onset of diabetic acidosis should be suspected in any known diabetic when unusual symptoms such as weakness abdominal pain, unusual constipation dyspnea or indeed any abnormal symptoms occur. It is essential to obtain urine immediately, by catheter if necessary, in order to test for diacetic acid as well as sugar. The patient suspected of having diabetic acidosis should be sent to the hospital since differential diagnosis may be difficult, especially in comatose patients.

Treatment—Prior to Hospital Admission.—While transfer to the hospital should be carried out early, treatment should be begun at home. A preliminary dose of insulin should be ordered by phone and if the distance to the hospital is considerable a second dose of crystalline insulin may be necessary on the way. The dose of insulin to be given at home varies with the previous dosage of insulin or may be from 30 to 100 units in a new case depending upon the phase of acidosis.

At Hospital.—Preparation at the hospital should include a warm bed and the provision of hot water bottles in order to conserve body heat. Apparatus is assembled for the giving of salt solution subcutaneously and intravenously and for the carrying out of gastric lavage and giving an enema. Upon the patient's arrival the hot water bottles are placed outside blankets so that burns on the skin will not occur. Blood and urine specimens are immediately obtained for analyses for blood sugar carbon dioxide, nonprotein nitrogen and blood chloride.

Insulin should be given immediately upon arrival. Two facts make judgment as to the dose to be given difficult. (a) Resistance to insulin increases rapidly as acidosis advances. (b) The law of diminishing returns applies to the efficiency of insulin so that the expected results from the second and succeeding doses may sometimes be obtained only by increasing the dose. High blood sugar levels of 700 to 1500 mg will justify large insulin dosage, whereas a child with newly discovered diabetes and a patient who may have received insulin at home may require much less insulin. Many a patient in diabetic coma receives sufficient insulin but owing to delays or indecision in the first two or three hours too little insulin is given at the time that it would count most. Insulin given six to ten hours after admission in an unconscious patient is probably worth unit per unit less than one third what it is

worth during the first hour after admission. The average adult drowsy with a systolic blood pressure over 100 mm might receive 50 to 100 units. A child with diabetes might need 20 to 40 units as an initial dose. However, in patients profoundly unconscious, in shock and dehydrated, usually 100 units should be given subcutaneously and 50 or more units given intravenously. The more rapid action of intravenously given insulin is well known. A second dose should probably be given within a half hour and perhaps repeated again within the hour. By the end of an hour some of the laboratory reports will be available and decision as to next dose may be made. Little fear need be had that too much insulin will be given in unconscious patients where the unconsciousness is due solely to diabetic coma. The danger of a rapid change from diabetic coma to hypoglycemia without warning symptoms is slight. Actually hypoglycemia is almost unknown in the first six hours of treatment of severe acidosis. If it occurs later it will not have serious consequences if treated properly with orange juice or intravenous administration of glucose.

Urine and blood tests should be done at least once in two to three hours and the insulin dose may be planned in the average case in accordance with a schedule like the following:

Benedict Reaction	Red	Orange	Yellow	Yellow-Green	Green	Blue
Insulin (units required)	24	20	16	8	0	0

Such a schedule would need alteration for the more severely ill patients. During the next few hours the clinical condition of the patient including particularly the mental state, type of breathing and the pulse, will help in deciding the dosage of insulin. No plan of treatment based on mathematical calculations of the blood sugar and carbon dioxide will take the place of constant bedside observation of the patient.

Maintenance of Fluid and Electrolyte Balance—Dehydration, hemoconcentration, falling blood pressure and reduced peripheral blood flow with consequent cold purplish extremities, dryness of the skin and softness of the eyeballs are distinguishing features of diabetic coma. Normal saline solution is given immediately, 1500 cc by vein and 1000 cc under the skin. In early diabetic acidosis the administration of hot broths in liberal quantity is advisable. Ordinarily most unconscious patients will require from 3000 to 6000 cc of normal salt solution but in exceptional cases 9000 cc of fluid in twenty-four hours have been given by Campbell, Reeser and Kepler¹⁰ and 13,000 cc by Root and Ruseman¹¹ in order to relieve anuria. Recovery from anuria in severe diabetic coma complicated by laryngeal obstruction was accomplished by the administration of 7000 cc of normal saline solution, 1500 cc of blood plasma and 250 cc of whole blood in twenty hours in addition to 3620 units of insulin in the case reported by Gorman, Harwood and

White¹² from the Massachusetts General Hospital. Actually if anuria is present the safe rule is to leave the needle in the vein of the arm or ankle and let salt solution flow continuously one liter per hour until the blood pressure rises and urinary secretion begins, provided it has been shown by blood chloride determinations that the anuria is due to ketosis, shock and the loss of chloride. Fluid by mouth is limited to 100 cc. per hour after the stomach has been washed out.

Transfusion with Whole Blood or Plasma—No loss of blood protein or plasma has occurred in uncomplicated diabetic coma. The effective agents in diabetic coma, namely insulin, water and salt, are effective because they replace definite deficiencies. A blood transfusion hardly seems likely to be of value in the uncomplicated case of diabetic coma.

Gastric Lavage—Usually the stomach of a patient in true diabetic coma is distended with a large amount of fluid containing food remnants and old blood, the result of bleeding from the stretched gastric mucosa. More than one patient in advanced coma has died with the diagnosis of pulmonary edema, when in reality the rales of the lungs were due to the aspiration of gastric content from a distended stomach. Drainage of the stomach therefore should always be done with a large Ewald tube and the stomach washed with warm water within the first hour after admission.

Enemas—A cleansing enema should be given and in severe cases repeated during the first few hours of treatment.

Food.—The administration of food in liquid and simple form should be begun whenever the improvement of the patient permits and provided the patient has no complications which would prevent it. At first 3 to 4 ounces of liquid including warm broth thin oatmeal gruel or tea with a little sugar or orange juice equivalent to 10 gm. per hour are used. In the first twenty four hours we aim at giving from 100 to 200 gm. of carbohydrate and a total of 30 to 50 gm. each of protein and fat in cases in which rapid improvement has occurred. Naturally in the severe unconscious patient food by mouth may not be possible for from twenty four to seventy two hours. In such cases the use of intravenous dextrose solution after a sufficient amount of insulin has been given may be used and repeated.

Alkalics—No alkalies are used in the treatment of coma patients at the Deaconess Hospital. Occasionally serious errors in the interpretation of a patient's condition have been made when a blood carbon dioxide value was made artificially high by the previous administration of alkali. In such instances caution must be used in interpreting the blood value.

Stimulants—Patients unconscious for several hours with low blood pressure, rapid weak pulse and cold mottled extremities may be given stimulants such as caffeine, epinephrine or transfusion. The benefits observed are not striking. The use of morphia or indeed the use of any

drug which may depress respiration should always be avoided in the treatment of pain in a patient with acidosis

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COMMON SENSE IN ALLERGY

Relation to Specific Treatment

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TREATMENT in the allergic diseases is perhaps less standardized than in any other group of medical conditions. This is not surprising where the fundamental cause of the allergic state is still unknown and where many possible sensitizing substances and a multiplicity of "shock organs" may lead to the appearance of different types of symptoms in various parts of the body. To these factors must be added a wide variation in technic and in interpretation of the typical methods of diagnostic procedure, namely the skin tests. Variation in the standardization of extracts used for both diagnosis and treatment is likewise confusing, for some clinics employ a total protein, others a total nitrogen basis on which to determine the strength of their materials. Such considerations emphasize the desirability of a careful evaluation of the allergic picture as a whole, keeping in mind the relationship of proposed allergic therapy to the general well being of the patient.

Diagnosis in allergy must be both differential and etiologic. The differential diagnosis should be considered first, for all are not necessarily allergic who sneeze, wheeze or itch. In the majority of instances however the patient has made his own correct diagnosis when he first comes to his physician and states that he is suffering from asthma, hay fever or hives. It is the etiologic diagnosis that is of paramount importance, for only in the careful search for the underlying trigger mechanism which sets off the patient's symptoms are we able to apply intelligently types of treatment which give the best chance of success.

Various weapons are at hand for an attack upon this etiologic or specific diagnosis. The most important of these is the *history*. It is usually possible to determine whether the patient falls into the hyper-sensitive group by the use of a modified detective technic coupled with a guided third degree questioning. Are his symptoms characteristic of allergy? Does he admit past or present manifestations of allergy other than his present important symptoms? Has he a positive family history for allergy? One or more leads may thus likewise be obtained as to the possible nature of the offending substance. Are the symptoms seasonal so that they may coincide with the pollination of trees in spring, the

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grasses in summer, or the weeds in fall? Do they run beyond the pollen seasons with flare-ups between them, suggesting molds as causative agents? Or are they present only with "colds" in winter? Are animals members of the family? What is the bedding made of? Is there evidence that foods have bothered recently or in the past? What is the patient's occupation, what his avocations? Can these be related to his symptoms? How about his medicines, what of nervous tension? These and often many other questions must be answered and recorded before any attempt is made to confirm one's clinical suspicions by skin tests.

How many tests should be done, by what methods, how should they be interpreted, what reliance placed upon their results? The reply to these questions could fill many pages. Even allergists would disagree upon the conclusions. As is the case in surgical technic, the answers depend upon the individual experience of the doctor, as well as upon the history which each patient presents, his probable degree of sensitivity, and the potency of the testing materials.

Certain principles based upon common sense are too often overlooked in the enthusiasm of the hunt. Scratch tests are harmless, they will never kill the patient. Intradermal tests are more delicate, of undoubted value, but are potential dynamite and should be used in experienced hands in suitable dilutions in modest numbers at any one sitting. They should not be done until a careful history has warned the operator of the degree of sensitivity which he is likely to expect.

The *interpretation* of skin tests is a difficult problem. It must be remembered that skin tests may be positive where there is no evidence of clinical sensitivity to the substance tested, and negative in cases of hypersensitiveness. Normal people frequently have skin tests which can be called "positive." Allergic people sometimes have negative skin tests. Moreover, one does not need to use a magnifying glass to detect a positive test. It is important to appreciate that the finding of positive skin tests which coincide with proved clinical sensitivity varies statistically in different types of cases. It is high, for instance, in seasonal hay fever, less so in perennial inhalant allergy, lower still in food allergy, and even lower in urticaria. What may we say then in favor of the value of skin tests as diagnostic weapons in allergy? They are valuable adjuncts with which to try to prove the leads that our allergic history has provided and they occasionally unearth allergens which clinical trial elimination proves to be of importance. The liability of skin tests must be appreciated as well as their assets.

The importance of making the specific diagnosis has been mentioned without emphasizing the fact that such a procedure is an integral part of treatment as well, for treatment in allergy must be based upon either elimination of the offending allergen or immunization against it by desensitization—either specific or nonspecific in nature. *Trial elimination* of suspected offending substances therefore becomes an integral part

mechanical factors of importance His nose showed only a mild moderately pale vasomotor rhinitis X-rays of the sinuses were negative His history and clinical picture had indicated the possibility of a mild dust inhalant hypersensitivity as a possible cause for his nasal symptoms Scratch tests had been negative, but among twenty intracutaneous tests there were moderate sized positive reactions to house dust, silk and wheat He had been placed upon a wheat-free diet, given detailed printed instructions for control of dust in his home, and advised to avoid exposure to silk at all times He had likewise been given a prescription for nose drops to relieve his symptoms Questioned about his interval progress on such a regimen, it developed that both the patient and his wife were scrupulously conscientious in the carrying out of their instructions Not only was the wheat-free diet followed to the letter, but it was decided that eating away from home would provide undue risk of failure of the experiment Exposure to silk, as well as to house dust, would be hard to avoid abroad, so the patient and his wife gave up the movies and all outside contacts His nose steadily became worse, the emotional situation more tense, his publishers were returning his stories unwanted The nose drops were used six or eight times in each twenty-four hours

Skin tests were repeated in the clinic and found to be essentially unchanged It was perfectly obvious that the cure in this instance had been far worse than the disease, as was emphasized when both the patient and his wife burst into tears upon being advised to seek out the nearest restaurant, have a big meal of anything they desired, and then go to the movies Discontinuation of the nose drops was recommended A month later, the patient's symptoms had almost subsided, his spirits had improved, and he stated that his publishers had accepted a short story

Comment—The original allergic studies appear adequate and the program of trial elimination justifiable Frequent periods of follow up would have demonstrated that the positive skin tests were not of clinical importance and that the general situation was getting out of control The subsidence of his symptoms could have been dependent upon the removal of the nose drops to which he may have become sensitive as well as to the relief from his previous emotional tension

Elimination or avoidance is not always possible or feasible in allergy This is particularly true in hay fever and in certain types of asthma. Specific desensitization is then indicated whenever possible The tendency here is to rely too implicitly upon positive skin tests, to make an extract consisting of all the test-positive substances, and to treat the patient with it. This is quite proper only to the extent that the patient's clinical history coincides with adequate evidence that he is exposed to the positive reactors, and that his symptoms are caused by them For example, many patients who have clinical ragweed hay fever, have positive skin tests to grasses as well as to ragweed, but have no symptoms in the grass season To include grasses in the treatment of such a case changes the character of the therapy from specific to nonspecific and, in the instances in which pollen mixtures are employed, reduces the concentration of the effective ragweed

Dosage in specific desensitization should vary with the sensitivity of each individual patient rather than be guided by routine instructions covering all patients Not all diabetics need the same amount of insulin,

nor does any given diabetic tolerate changes in dosage prescribed on other than an individual basis. In like manner not all allergic patients obtain optimum results on standardized doses. The hay fever sufferer of average sensitivity may do well on an average schedule, but the patient with a high degree of sensitivity may have recurrent constitutional or severe local reactions while the one with slight sensitivity may receive no benefit on the same dosage regimen. Some of the unsatisfactory results in hay fever therapy are due not so much to the inadequacy of the many excellent available extracts for treatment as to error in the selection of the proper specific pollens required, and failure to give optimum dosage.

The *size of the local reaction* following treatment is the best guide to the determination of the amount of the next dose. The patient should be instructed to observe all local reactions as well as any generalized symptoms, however mild, such as itching, sneezing or wheezing. Such observations will act as a warning signal advising caution against an immediate increase of dosage. Last year's record is a great aid in this year's treatment. Many doses may be saved or higher concentrations reached as the physician becomes more familiar with the patient's degree of tolerance.

CASE III.—Mrs F. B. T., aged 32, gave a history of typical ragweed hay fever of four years duration confirmed by large positive skin tests by the scratch method in dilutions as high as 1:5000. An initial high dilution ragweed extract with a chart and conservative dosage schedule was sent to the patient's local doctor with the request that it be returned after six doses had been given, with comments as to the local reactions. In the middle of the ragweed season the patient appeared with severe hay fever. Inquiries as to her treatment divulged the fact that the first three inoculations gave no local reactions. Her doctor had therefore stated that the material could not be any good and that further treatment was useless.

Comment—Early dosage may possibly be too conservative—or too excessive—in a new patient, but such a fault is easily remedied without discontinuing treatment if there is mutual cooperation between the physician and patient.

In instances where *infection* plays the leading role, particularly when the onset of symptoms comes in or after middle age, skin tests are frequently noncontributory. Whether or not the mechanism which produces asthma in these cases is due to a true bacterial allergy, the eradication of a focus of infection is frequently followed by remission of symptoms which is sometimes permanent.

CASE IV.—M. M. B., a 49 year old leather worker was well until September 1945 when he developed a head cold, productive cough and, several weeks later severe asthma. During the next four months he was treated at home and in two different hospitals with varied therapy including the removal of all teeth the in

halation of oxygen and oxygen-helium mixtures under positive pressure, adrenalin by all routes including aerosols, aminophylline by mouth, vein and rectum, iodides, one course of sulfadiazine and one of intramuscular penicillin. In spite of all these measures his asthma persisted.

He was first seen by us in early February, 1946, in severe status asthmaticus and was immediately admitted to the hospital for emergency treatment. This consisted of intravenous fluids including aminophylline, oxygen inhalation, sedation, large doses of potassium iodide, and a bronchoscopy, during which several ounces of mucopurulent tenacious sputum were aspirated. Within seventy-two hours the patient had reverted to a condition of severe asthma necessitating an average of eight hypodermic injections of 0.5 cc of adrenalin in twenty-four hours.

Physical examination was not remarkable except for the presence of typical rather "tight" asthmatic breathing. No history of probable extrinsic sensitivity could be elicited. The family history was negative for allergy. Twenty-five intracutaneous skin tests to common foods, dusts and pollens failed to react. The temperature was normal, the white blood cells 30,000, with 18 per cent of eosinophils in the blood smear. X-rays of the sinuses showed slight thickening of the antra and ethmoids with no retained secretion. Chest x-rays and bronchograms gave no clear-cut evidence of bronchiectasis, but rather of a pulmonary fibrosis. The patient consistently raised about 3 ounces of tenacious mucopurulent sputum daily which at first showed a pure culture of *Bacillus pyocyaneus*, and the same organism was found in the culture of secretion removed from his bronchi by bronchoscopy.

Varied efforts were made to control the patient's pulmonary infection during his three months of hospitalization. Among these was the administration of 2 Gm of sulfadiazine which was followed in three hours by a series of shaking chills and an elevation of temperature to 105° F by mouth. This was followed by an increase of purulent sputum and the obtaining of a sputum culture of Type III pneumococcus, but by no changes in his chest signs or in his chest x-ray. Intramuscular penicillin in doses of 20,000 units every three hours was then started. The temperature returned to normal in twenty-four hours and the asthma gradually disappeared. He continued to raise 3 ounces of purulent sputum daily which now gave a positive culture for alpha hemolytic streptococcus and, several days later, one for *Bacillus coli*. At the end of ten days the asthma recurred with its former intensity in spite of continued penicillin therapy. The white counts during this period had varied between 35,000 and 20,000 with sedimentation rates in the neighborhood of 30 mm in one hour.

At this point, streptomycin therapy was instituted and continued for five days in doses of 1 gm. daily, divided into intramuscular injections at three-hour intervals. At the termination of this treatment no change was observed in the patient's condition, but within the next eight days his cough, sputum and asthma gradually disappeared, his white count and sedimentation rate fell to normal, and his sputum culture became negative for bacteria. He was discharged to his home symptom-free the following week. A follow-up one month later indicated that he was still without trouble.

Comment—The exacerbation in this patient's asthma following sulfadiazine, to which he had apparently become sensitized in a previous course of treatment, was undoubtedly due to the fever accompanying the drug reaction. It is important that his cough, sputum, white count and sedimentation rate remained elevated during this period of freedom from his wheezing and that his asthma recurred. A prolonged follow-up period is necessary before an optimistic prognosis is war-

When in such cases, in spite of evidence that this patient's chronic pulmonary infection is under control, it is evident that a seemingly minor respiratory infection may reactivate his process and project him again into severe chronic asthma.

CONCLUSIONS

These cases have been presented in an attempt to illustrate a few of the pitfalls encountered in the handling of some types of chronic allergic disease. Variation in interpretation of diagnostic evidence must be expected and encouraged for it is only by such means that continued progress may be expected in a field that is still young. Yet constant watchfulness in the form of frequent and prolonged supervision must be exercised in order that specialized procedures of investigation and treatment may at all times coincide with the principles of good general medicine and sound common sense.

CLINICAL APPRAISAL OF DEMEROL, BENADRYL AND PYRIBENZAMINE

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ATTENTION has been recently focused on three important synthetic drugs which have considerable clinical importance. Demerol has already been subjected to critical investigation and has proved an effective antispasmodic agent which also possesses a notable sedative and analgesic effect. The other two preparations, benadryl and pyribenzamine, have not yet received widespread clinical use. The early reports, however, in a field where therapy has been limited, are so encouraging that they are worthy of review at this time.

DEMEROL

In the course of investigating a series of synthetic compounds having an atropine-like action, Eisleb and Schaumann,¹ in 1939, discovered a preparation, 1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester hydrochloride, which has since been named demerol. In addition to an antagonistic action against acetylcholine, it was noted that the drug possessed an analgesic effect and a direct depressant action on smooth muscle. Pharmacologic and clinical studies soon confirmed the efficacy of the compound.

In this country extensive clinical studies were made by Batterman and his co-workers,^{2, 3, 4} who found that demerol was both safe and effective. No specific contraindications to its use were noted except for rare hypersensitive individuals. Diseases involving the kidney and liver, and anemia do not preclude its use. Minor side effects are not uncommon, especially in ambulatory patients, but they are usually not of such severity as to demand that the drug be discontinued. In many instances the side effects disappear while the drug is still being administered. Caution is indicated when the drug is given in the presence of intracranial lesions, since in these cases respiratory depression may occur,⁵ and demerol should not be used indiscriminately in the treatment of diseases which tend to run a chronic course, since there is a possibility of habituation to the drug. It must be noted, however, that

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the tendency to addiction is considerably less than with morphine. Demerol is subject to the regulations of the Federal Bureau of Narcotics.

Dose and Method of Administration—The average effective dose of demerol administered orally or intramuscularly is 100 mg.² The dosage may vary from 50 to 200 mg., and may be repeated at two three and four hour intervals. The drug is approximately twice as effective when given by the intramuscular route as compared with oral administration. The sedative and analgesic effect of a 100 mg. dose injected intramuscularly is roughly equivalent to the effect produced by 10 mg. ($\frac{3}{8}$ gram) of morphine. The amount of relief afforded also varies with the intensity and the type of pain present. As might be expected, the more severe types of pain require larger doses repeated at more frequent intervals. In general, pain arising from disturbed visceral function is relieved more easily and by smaller doses of demerol than the pain arising from skeletal disorders. In some individuals it is necessary to use small supplemental doses of morphine and in a few cases, for no apparent reason, the drug is not effective. Relief is usually achieved within fifteen minutes when the intramuscular route is employed, whereas a longer and more irregular period is required for an effect when the drug is given by mouth. The relief thus afforded usually persists for about three hours but this again varies with the nature and the severity of the pain. The subcutaneous injection of demerol is irritating and there is rarely need for its intravenous injection so that these routes of administration are not recommended.

Clinical Use—Because of its spasmolytic property combined with a sedative and analgesic effect, demerol has been employed in a wide variety of medical and surgical conditions which previously required the use of opiates. The drug has several advantages over morphine. It is much less likely to produce habituation or addiction, and only rarely does it cause respiratory depression. The latter is extremely important in many patients not only because normal respiratory activity favors adequate oxygenation of the blood, but also because it promotes the venous return of blood to the heart, thus helping to prevent the stasis of blood in the lower extremities. It is well known that slowing of the venous circulation may lead to intravascular clotting of blood and subsequent pulmonary embolism. For this reason we have found demerol especially helpful in relieving the pain and distress due to myocardial infarction. When the distress is severe, a dose of 150 mg. may be given intramuscularly and repeated at two hour intervals for two to three doses until relief is achieved. The dose is then reduced to 100 mg. injected at three to four hour intervals. In some instances small supplemental doses of morphine may be necessary since the 150 mg. dose should not be repeated frequently at short intervals. As there is a significant incidence of pulmonary embolism complicating

myocardial infarction in which the embolus does not arise from the heart, it would appear prudent to utilize all measures which will lessen venous stasis in the lower extremities

In the treatment of acute paroxysms of *bronchial asthma*, morphine is contraindicated and the problem of sedation is frequently a trying one. Pharmacologic studies have indicated that demerol possesses the property of relaxing the tracheobronchial tree, and it does not depress the respirations or the cough reflex, though the sputum may become slightly more viscid.

It is not surprising then that the drug has been used successfully as an adjunct in the treatment of acute paroxysms of bronchial asthma,^{6,7} and it may be prescribed in doses of 50 to 100 mg. as often as every three hours. Although it has been advocated in chronic continuing asthma, it is probably best to avoid its use under these circumstances because of the danger of habituation and the availability of other therapeutic agents.

The relief of *gastrointestinal, biliary and renal colic* from the administration of demerol has been striking because of its antispasmodic action, and in this respect it differs from morphine, which causes increased gastrointestinal tone and biliary spasm, which is not relieved by atropine. The following case report is of interest to illustrate this point.

A V, a 62 year old, white, married male, was admitted to the hospital on February 25, 1946, because of urinary retention, secondary to an enlarged prostate. In the course of his preoperative study, despite the fact that he had only occasional symptoms that might have been referable to a disordered biliary system, x-rays revealed that he had gallstones. A transurethral prostatectomy was planned, since relief of the urinary obstruction was the more immediate problem. Accordingly, morphine sulfate, 10 mg. ($\frac{1}{6}$ grain), and atropine sulfate, 0.4 mg. ($\frac{1}{150}$ grain), were injected subcutaneously for preoperative medication. About twenty minutes after the injection of the medication, he was suddenly seized with a pain in the right upper quadrant which gradually increased in intensity and then began to radiate along the right costal margin and finally through to the back. The pain was accompanied by profuse perspiration and a moderate fall in blood pressure. The pain persisted for about forty minutes, then wore off without any residual distress. Physical examination failed to reveal any abnormal findings, and the electrocardiogram showed no abnormalities except a marked degree of left axis deviation. It was concluded that he had suffered an attack of biliary colic probably induced by the administration of morphine. Two days later he was prepared for operation with 100 mg. of demerol and 0.4 mg. ($\frac{1}{150}$ grain) of atropine, and his operation, subsequent course and convalescence were uneventful. Needless to say, demerol was also prescribed for his postoperative distress.

The problem of analgesia in *obstetrics* has become increasingly important, and here again demerol has been very useful. The intramuscular injection of 100 to 150 mg. when labor is well under way produces an effective analgesia, usually without any apparent interruption

in the progress of labor. The drug may be repeated at three hour intervals, providing delivery is not imminent. In some clinics other drugs such as scopolamine⁸ and barbiturates⁹ are combined with demerol. There is usually no untoward effect on the fetus unless the medication is given within two hours before birth.

Demerol has likewise been very helpful in preparing patients for operation⁴ and for the relief of pain and distress in the postoperative period.³ It is less likely to cause urinary retention or constipation than the opiates when administered to postoperative patients. The usual dose is 100 mg. given intramuscularly every three to four hours.

Side Effects—Minor side effects are fairly common, especially in ambulatory cases and with parenteral administration. Among these, dizziness and giddiness are the most commonly observed. Nausea, vomiting and a sensation of dryness in the mouth may also occur. These symptoms, as a rule, do not preclude the administration of the drug. In some instances more severe reactions occur, characterized by extreme weakness, marked dizziness, vomiting, sweating and syncope. Repeated large doses may cause cerebral irritation or convulsions.

Summary—Demerol is a synthetic antispasmodic drug with an analgesic and sedative action. When administered in doses of 100 mg. intramuscularly or orally at two or four hour intervals, it may be used for conditions which previously required opiates. It possesses advantages over morphine because it causes little, if any, respiratory depression, and is much less likely to be habit forming. Constipation and urinary retention in postoperative patients are more uncommon following the use of demerol than after morphine. The drug is contra-indicated only in rare hypersensitive patients but caution should be observed in patients with intracranial injuries because of the danger of respiratory depression in these patients. It should also be used cautiously in patients who are ambulatory and those with chronic diseases. The most common side effects are dizziness and giddiness with occasional nausea and vomiting. In many instances they are not so severe that the drug must be discontinued.

BENADRYL

In view of the gradually accumulating evidence that some features of the allergic reaction may be associated with the liberation of histamine, investigation has been directed towards synthesizing compounds that might counteract certain pharmacologic effects of histamine. Several such substances have been studied within the past few years but because of their toxicity have proved unsuitable for clinical use. Code¹⁰ has recently contributed an excellent historical review of these compounds. Loew and his associates^{11, 12} and others¹³ have studied a number of compounds some of which possessed a high anti-histamine activity and relatively low toxicity in animal experiments.

Two of these substances have received clinical trial and have been named benadryl and pyribenzamine, respectively. It appears likely that in the future more compounds in this series will be discovered that may prove to have an even greater pharmacological activity.

Benadryl (beta-dimethylaminoethyl benzhydryl ether hydrochloride) is one of a series of synthetic compounds which has, in addition to an antispasmodic effect, the property of counteracting some of the pharmacological actions of histamine. Preliminary study in animals has indicated a relatively low toxicity.

While the drug has not been subjected to widespread clinical use, the early reports indicate that it may be ingested in moderate amounts over long periods of time without untoward effects. No skin eruptions or febrile disturbances have been reported following its use and it is not habit forming.

Dose and Method of Administration.—Benadryl has been administered orally, intramuscularly and intravenously and is available in capsules of 50 mg and as an elixir with 10 mg of benadryl in 4 cc (3i) of the mixture. The average adult oral dose is 50 mg, repeated three to four times a day, and the total daily dose has varied from 50 to 500 mg. The elixir of benadryl in doses of 10 or 20 mg (one or two teaspoonfuls), repeated three to four times a day, may be given to children. Logan¹⁴ has advised using a daily amount of 2 mg per pound of body weight divided into two to four doses. The amount of drug required will vary with the severity of the allergic symptoms. When there is marked distress, a dose of 100 mg of benadryl may be necessary, three to four times daily, or 50 mg may be given six to eight times during the twenty-four hour period. As the symptoms are ameliorated, only one-half the average dose may be required for continued freedom from distress.

The drug is not curative and the symptoms recur when it is discontinued. No evidence is available to suggest a delayed or cumulative effect. Because drowsiness is encountered in a number of cases, it is well to avoid the concomitant use of sedatives and hypnotics. When the drowsiness is bothersome, it may be counteracted in some cases by the simultaneous administration of ephedrine sulfate or benzedrine. Since there is evidence that benadryl potentiates the action of ephedrine, the combination of these two drugs may prove even more effective. Intramuscular injection of benadryl frequently causes pain and this route of administration is not recommended. While the drug has been diluted in isotonic saline and injected intravenously, in most instances this route of administration is unnecessary. We have given 30 mg doses of benadryl dissolved in 50 cc of normal saline and injected over a period of four to six minutes without untoward effects.

Clinical Use.—Benadryl has been used with varying success in a variety of allergic diseases presumably because of its antihistamine

effect, and it has also been administered in a number of other conditions because of its antispasmodic action

Hay Fever and Vasomotor Rhinitis—Koelsche, Prickman and Carver¹⁵ treated fifty two patients with hay fever and obtained over 50 per cent improvement in three-fourths of the cases. The dosage employed was 50 to 100 mg. administered by mouth three times daily. Ten of the group obtained almost complete relief with cessation of nasal discharge, and relief of the irritating feeling in the nose and eyes. In the majority of cases a larger dose is unnecessary. The effect is usually apparent within sixty minutes after the ingestion of the drug, and persists for about five to eight hours. Combining ephedrine sulfate, 22 mg. ($\frac{3}{8}$ grain), with the benadryl produces an increased amount of relief.

McElm and Horton¹⁶ also treated twenty two cases of hay fever and achieved over 50 per cent improvement in all but one case. It appears then that in many cases considerable relief from the acute symptoms of hay fever may be expected from the use of benadryl while treatment is being administered, and that these symptoms will recur if the drug is discontinued. There is nothing to be gained by taking the drug out of season. Williams¹⁷ treated twelve patients with perennial vasomotor rhinitis, and of these ten obtained 90 per cent relief. The two patients who failed to obtain relief were unable to continue with the medicine because of severe dizziness.

Urticaria—Curtis and Owens¹⁸ prescribed benadryl for eighteen patients with various types of urticarial eruptions and eleven patients had complete disappearance of the urticaria during treatment. Four patients did not respond to the usual dosage of 50 to 100 mg. given orally one to five times daily.

In treating cases of chronic urticaria, angioneurotic edema and dermographia, when the drug was discontinued there was prompt recurrence of the disease.

O'Leary and Farber¹⁹ followed fifty patients with acute and chronic urticaria using approximately the same dosage schedule of benadryl outlined above, and they achieved similar results. Nine of fifteen patients with acute urticaria experienced prompt relief, five were improved, and only one received no benefit from the treatment.

Of the first fifty two cases treated by Todd,²⁰ forty seven were completely relieved, four were partially relieved, and one was relieved of whealing, but not of pruritus.

From these experiences, it appears that benadryl is highly effective in the treatment of angioneurotic edema and urticaria when administered orally in 50 to 100 mg. doses repeated two to six times a day. In the majority of cases relief is achieved only while the drug is being administered.

Urticaria occurring in serum sickness and following liver injections

or penicillin therapy has also been controlled by the use of benadryl. In some instances the relief thus afforded allowed continued injections of the medication.

Asthma—Koelsche, Prickman and Carryer¹⁵ administered benadryl to twelve patients with bronchial asthma with results that were not encouraging. Only four reported relief following the use of the drug, and it was felt that considerably more experience would be necessary before any conclusions could be drawn. Our limited experience in the treatment of asthma with benadryl has likewise been disappointing although in a few cases the administration of ephedrine and benadryl at bedtime decreased the number of nocturnal attacks and allowed more restful sleep. More recently reports are accumulating in which relief has been obtained in a higher percentage of asthmatic patients, but it is apparent that carefully controlled studies will be necessary to determine the status of benadryl in the treatment of asthmatic paroxysms. In some instances the asthmatic symptoms appear to increase slightly in intensity after the drug is discontinued.²¹ It is of interest that we^{22, 23} have been able to demonstrate complete protection following the intravenous use of the drug against histamine-induced asthmatic-like attacks in certain asthmatic subjects.

Miscellaneous Uses—Benadryl has been prescribed in a variety of other unrelated conditions to achieve an antihistamine or an antispasmodic effect. Amongst these disorders are contact dermatitis, migraine, Ménière's syndrome, erythema multiforme and dysmenorrhea. Whether it will prove effective in these and in other conditions is not clear, and its effectiveness will undoubtedly be the subject of future studies.

Side Reactions—Drowsiness is the commonest side effect produced by the administration of the drug. Dizziness, nervousness and a dry mouth are also experienced, and in some instances nausea, weakness, dilated pupils and tingling sensations have occurred. Reactions are more common when the 100 mg dose is prescribed, and they frequently disappear when the dose is reduced. In some instances side effects disappear while the medication is being continued, and in other cases the administration of benadryl must be stopped.

Summary—Benadryl is one of a series of new compounds of low toxicity having the property of counteracting many of the pharmacologic effects of histamine. It also has an antispasmodic action. The drug has been used effectively in doses of 50 to 100 mg administered by mouth two to five times daily for the relief of hay fever, perennial vasomotor rhinitis, urticaria and angioneurotic edema. Success has been limited in the treatment of bronchial asthma, and further study will be necessary to define its value. Benadryl has also been prescribed for a variety of other conditions, such as contact dermatitis, erythema multiforme, migraine, Ménière's syndrome and dysmenorrhea, but its proper place in the therapy of these conditions remain to be evaluated. Minor

side reactions are not uncommon and amongst these drowsiness is the most prominent. Dizziness, nervousness dryness in the mouth, and nausea may also be experienced.

In some instances the drug must be stopped because of the side effects, and in other cases they tend to disappear while the medication is continued. Benadryl may be used over relatively long periods of time without cumulative effect or notable systemic reactions. While it is evident that remarkable success has been achieved with benadryl in alleviating the symptoms of hay fever and urticaria, it must be noted that the drug is not a cure-all. Final judgment must be reserved concerning its exact place among drugs effective in the treatment of allergic disorders.

PYRIBENZAMINE

Pyribenzamine (N' pyridyl N'benzyl N-dimethyl ethylenediamine monohydrochloride) is a synthetic compound which manifests a pronounced capacity to prevent many of the pharmacological actions of histamine. Experimental work in animals indicates that its activities are similar to benadryl and that it has relatively low toxicity.²⁴⁻²⁵ Clinical studies have not been as extensive to date as those made with benadryl, and no comparison of the two products may yet be made. Studies in animals and man receiving pyribenzamine over notable periods of time have failed to reveal any untoward effects or the development of any significant tolerance to the drug. The exact mode of action is unknown.

Dose and Method of Administration.—The average adult oral dose of pyribenzamine is 50 mg. repeated four times daily, preferably after meals. The total dose in adults has varied from 50 to 600 mg., depending on the severity of the allergic symptoms. It is well to use the smallest effective dose, since the number of side reactions may increase with an increase in the amount of pyribenzamine prescribed. In children a dose of 10 to 25 mg. repeated three to four times daily may be effective. The subcutaneous and intramuscular injection may cause some local necrosis of tissue and is at present not recommended. When pyribenzamine is given by the intravenous route in animals it has a significant hypotensive effect and hence this route is not advised in humans until further studies are made. The drug is available in tablets of 25 to 50 mg. and suppositories of 50 and 100 mg., respectively.

Clinical Use.—While many clinics are engaged in an extended study of the use of pyribenzamine in varied allergic disorders the only completed study available is that of Arbesman and Koepf,²⁶ which included 277 patients. They noted that relief of symptoms occurred within fifteen to twenty minutes, and persisted for four to six hours after the ingestion of pyribenzamine. In some instances a total daily dose of as much as 1000 mg. was given without untoward effect, and in many

cases administration of smaller doses was carried on over a period of nine months with no ill effects. The experience with hay fever and urticaria treated with pyribenzamine was very similar to the benadryl studies. Thus, of 140 patients afflicted with *grass* and *ragweed* hay fever, 85 per cent had relief of symptoms. Of fifteen patients with *acute urticaria*, all but one were notably relieved of symptoms. There were forty-four patients with *chronic urticaria* and of these, 63 per cent were improved after taking pyribenzamine. The results of treatment of *bronchial asthma* were not as satisfactory, but 46 per cent noted definite relief of bronchial symptoms. When ephedrine sulfate and pyribenzamine were administered together a more notable improvement was obtained.²⁷ Our experience²⁸ using the drug to protect against histamine-induced asthmatic attacks in certain asthmatic subjects also demonstrated a varied protection from complete to none at all when pyribenzamine was given by mouth. The effects of physical allergy and constitutional reactions occurring in hyposensitization therapy could also be ameliorated or prevented by oral administration of the drug. Lowell has used pyribenzamine effectively in the treatment of *poison ivy*, especially to relieve the itching. Its effect on the progression of the lesions was not clear.

Side Reactions—Side effects are common, but rarely serious, and in many cases do not demand that pyribenzamine be discontinued. The larger the dose employed, the more frequent will be the side effects. Drowsiness, dizziness, faintness, nausea and vomiting are the more common undesired effects. In some instances nervousness, drying of the mouth, and palpitation may be experienced.

Summary.—Pyribenzamine like benadryl is one of a series of new synthetic compounds of low toxicity having the property of counteracting many of the pharmacologic effects of histamine. It may be used for extended periods of time without ill effects. It has been used effectively in 50 to 150 mg. doses, repeated three to four times a day, in the treatment of hay fever and urticaria. Pyribenzamine has been less effective in the treatment of bronchial asthma and further study is needed to determine its exact value in this disease state. Minor side effects are common and may increase in number and severity with higher doses of the drug. Sleepiness, dizziness, nausea, vomiting, nervousness and palpitation are the most common undesired effects. In some instances the drug must be discontinued. Further studies undoubtedly will indicate whether benadryl or pyribenzamine is superior for the treatment of allergic diseases, and which drug will produce fewer side reactions. There appears to be a marked similarity between the two drugs.

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CHEMOTHERAPY IN DISEASES OF EAR, NOSE AND THROAT

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WITH the advent of chemotherapy, otolaryngological practice has undergone revolutionary changes. The axiomatic surgical principles of a decade ago are today obsolescent. For example, in certain grave complications resulting from otitic and sinus complications, surgery is no longer our first thought but rather the patient is fortified with either the sulfonamides or penicillin, or both and the optimum time is selected for surgical intervention.

While the demand for surgery in the management of otolaryngological infections is clear cut and urgent, under certain conditions, it will be generally agreed that much of the surgical treatment of ten years ago has now become medical treatment.

Bacteriology today has assumed an essential role in the successful treatment of ear nose and throat infections. Formerly bacteriological data were a valued influence in determining the surgical procedure, the course of the disease, and its prognosis. For example, the hazards of pneumococcus Type III in otitic infections will be well remembered. Certain patients who apparently were progressing favorably were abruptly seized with meningitis which usually proved fatal within seventy two hours.

With the selectivity of present day antibiotic agents a thorough going and detailed bacteriological study is imperative to the successful and intelligent management of otolaryngological infections. For example (1) Since gram negative organisms are frequently found in chronic otitic suppurative disease and since these organisms are immune to penicillin there obviously can be no benefit derived from this antibiotic agent in chronic suppurative otitis media with gram negative organisms present. (2) Since the sulfonamides have limited value in staphylococcal infections, early recognition of the staphylococcus is essential so that penicillin therapy may be instituted. (3) Certain strains of streptococcus are resistant to the sulfonamides but sensitive to penicillin.

It should be stated regarding penicillin that no other antibiotic agent has its range of usefulness in infections and its safety to the host. In

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approximately 2 per cent of the cases, however, it produces urticaria. A case in which I was consulted may be worthy of mention. A 30 year old nurse with otitis media was treated with penicillin in a suburban hospital. She developed a most severe generalized urticaria and an edema of the larynx. While tracheotomy was considered for several hours, she recovered without it under adrenalin, oxygen therapy and humidified air.

ACUTE SUPPURATIVE OTITIS MEDIA

This condition, so frequently complicating upper respiratory infections, appearing in approximately 20 per cent of all cases of scarlet fever, occurring often in measles and occasionally the result of swimming and diving, has long been respected for its potential hazards. The three intracranial complications, (1) lateral sinus thrombosis, (2) meningitis and (3) brain abscess, and such other complications as petrositis and bacteremia, are a constant threat in acute suppurative otitis media and have accounted for much morbidity and considerable mortality.

A survey of the literature on the treatment of acute suppurative otitis media with penicillin leads one to conclude that it is most effective. Our experience on the Otological Service at the Massachusetts Memorial Hospital with penicillin therapy in acute otitis media has been so satisfactory that the treatment has now become routine.

Procedure—If the patient on admission to the wards is found to have a bulging drum, a paracentesis is done at once. Cultures are then taken from the aural discharge, and 20,000 units of penicillin are administered intramuscularly. Ten thousand to 20,000 units of penicillin, depending on the age of the patient and the severity of the infection, are then given intramuscularly every three hours, day and night. The discharge from the ear will cease in approximately three days. The penicillin should be continued for three to five days after the ear stops draining and the condition by examination appears cured. Failure to continue treatment after cessation of the discharge will result in many recurrences of the infection. While certain test cases have been treated successfully by us without paracentesis, I am of the conviction that a bulging drum should be incised.

Under the regimen as described, no case received and treated by us in the early invasive stage of the disease has come to mastoidectomy. Allman and others have recorded similar experiences. Because certain strains of streptococcus are immune, and the staphylococcus is resistant to the sulfonamides, we are now using penicillin exclusively in acute otitis media. Recently we have been using penicillin in oil, in certain cases giving two injections daily and in others only one. Thus far the results are entirely satisfactory but too few cases have been

treated to draw conclusions Penicillin by mouth is effective if given in dosages three to five times the intramuscular dosage Where possible however I believe that hospitalization and intramuscular injections are preferable to oral administration

ACUTE SURGICAL MASTOIDITIS

The incidence of acute surgical mastoiditis has greatly lessened throughout the country due I am convinced, to the efficacy of penicillin and the sulfonamides



Fig 145.—A, The primary closure with catheter in place B the bandaged wound, with catheter easily accessible C the method of administering penicillin

Management of these cases in our clinic has for several years consisted in a careful extensive exenteration of the mastoid cavity and primary suture of the wound. With this technic we formerly employed sulfadiazine but for the last two years penicillin has been used routinely. The wound is closed in two layers using a continuous catgut suture for the subcutaneous tissues, and skin clips. A No 4 or 5 ureteral catheter is inserted into the antrum and the distal end brought out through the bandage and 10 000 units of penicillin are injected into

the catheter every eight hours and 10,000 units given intramuscularly every three hours. The first dressing is done on the fourth day, the skin clips are removed on the fifth day, and the patient is discharged usually on the seventh day (Fig 145)

CHRONIC SUPPURATIVE OTITIS MEDIA

The cause of chronic suppurative otitis media is usually *neglect*. In other words, the patient should have had a simple mastoidectomy four weeks after the initial onset of acute otitis media.

In our experience gram-negative as well as gram-positive organisms are present in this condition, and therefore it has not been cured by penicillin or the sulfa drugs. We have employed urethane and sulfanilamide in a few instances. While in some cases discharge ceased and negative cultures were obtained under this treatment, it was found within a few days or weeks that the gram-negative organisms had reappeared. More study with urethane is necessary to permit conclusions to be drawn. Currently we employ an endaural radical mastoidectomy in cases of chronic suppurative otitis media with cholesteatoma.

MENINGITIS OF OTITIC ORIGIN

The treatment of otitic meningitis is both surgical and medical. Lumbar puncture is first carried out for purposes of spinal fluid study and to bring the spinal fluid pressure down to normal limits. The patient is given large doses of sulfadiazine orally and penicillin intramuscularly. Penicillin when given intramuscularly does not reach the spinal fluid in adequate quantities to be effective, but the sulfadiazine gives a spinal fluid level approximately one half that of the blood. Penicillin is also given intrathecally. It is essential to eradicate thoroughly the otitic focus by surgery. With a patient in whom the meningeal infection is improving under antibiotic therapy, it is sometimes a temptation to discard the thought of surgery. This is a great error as the chance of a recurrent meningitis from an active otitic focus is always present.

CHEMOTHERAPY IN THE FIELD OF RHINOLARYNGOLOGY

The value of penicillin and the sulfonamides in infections of the nose and throat is as striking as it is in otitic infections, penicillin, however, being definitely the agent of choice.

Acute Sinusitis—While it has been repeatedly demonstrated that the majority of uncomplicated cases of moderately severe acute sinusitis will resolve under a regimen of bed rest and an isotonic shrinking spray, the supplementation of this regimen by either penicillin or sulfadiazine will, in the opinion of most workers, (1) greatly shorten the course of the disease, (2) markedly lessen the incidence of complications, (3) substantially curtail the number of cases requiring surgery, and (4) if surgery is indicated, result in a need for a less formidable

type of operation than otherwise to produce a cure. In acute sinusitis the penicillin is given intramuscularly every three hours in doses ranging from 10 000 to 20 000 units depending on the severity of the infection. Sulfadiazine may be given with confidence in its efficacy but our experience with penicillin has made it the agent of choice. In staphylococcal infections it is wise to institute penicillin therapy at once (Local penicillin catheter technic is explained under the heading "Osteomyelitis of the Frontal Bone.")

Orbital Cellulitis is one of the four most hazardous complications of acute sinusitis. This entity appears to respond especially satisfactorily to penicillin. In our clinic 75 per cent of patients with this complication recovered in the pre-sulfa and penicillin era without recourse to surgery. Since the advent of penicillin however only one such case has come to surgery and that required merely incision and drainage to effect a cure.

Osteomyelitis of the Frontal Bone complicating sinusitis is one of the most devastating lesions to be found in human pathology. It is characterized by a white, doughy edema over the forehead. This symptom has led to the frequently quoted statement of Mosher, "The diagnosis of osteomyelitis of the frontal bone is written across the brow." This disease, until two decades ago carried a mortality of nearly 100 per cent. With the Furstenburg operation, or some modification of it, the mortality was greatly reduced. The operation was grossly disfiguring, however requiring weeks or months of hospitalization, and approximately six months after the cure, the patient reentered the hospital for plastic surgery using either bone grafts vitallium or tantalum to fill the defect in the skull. We have had, in the past nineteen such cases in which we have performed this radical operation. About half of the patients in this series entered the hospital with either subdural or brain abscesses which invariably complicate osteomyelitis when the condition is not recognized early and adequate treatment is deferred.

With present day antibiotic agents and early recognition of the disease, it is doubtful if such radical surgery will again be necessary. We are employing both sulfadiazine and penicillin in large doses. Let me briefly cite two cases.

CASE I—A 10 year old boy who had been swimming arrived at the hospital with a right pansinusitis, a right orbital cellulitis, and frontal edema. He had been ill ten days. A ray revealed an early osteomyelitis of the frontal bone. The patient was fortified with both sulfadiazine and penicillin preoperatively. A small incision was made in the right eyebrow and a button hole opening in the floor of the frontal sinus was made. Through a small catheter the pus was gently washed from the sinus and a ureteral catheter placed there and held in situ with a suture. Ten thousand units of penicillin were instilled into the sinus every eight hours. The antrum was irrigated through the inferior meatus and a ureteral catheter inserted in the antrum and held securely there. Local penicillin was instilled into the antrum every eight hours through the catheter in the same manner and dosage.

as we employed with the frontal infection. In addition to the local therapy, penicillin was given intramuscularly and sulfadiazine by mouth. The patient left the hospital cured after ten days and remained well.

CASE II—A 28 year old man entered the hospital with a left pansinusitis or osteomyelitis of the frontal bone, a huge extradural abscess over the frontal lobe, and bacteremia. The patient was liberally fortified with sulfadiazine and penicillin preoperatively. A left modified radical frontal operation was performed—the posterior wall of the frontal sinus was widely removed to drain the extradural abscess. The wound was left open and the dura covered with sulfadiazine powder. Both penicillin and sulfadiazine were given systematically. On the eleventh post-operative day cultures from the wound were negative and it was sutured. The wound healed by first intention, and the patient left the hospital on the sixteenth day.

PHARYNGEAL INFECTIONS

Acute Tonsillitis has responded readily to either the sulfonamides or penicillin in our clinic.

Peritonsillar Abscesses, so frequently seen in the past, are now a rarity. In the very early stages of peritonsillar infection either sulfadiazine or penicillin is given.

Pharyngomaxillary Fossae infections with their hazardous sequelae are treated with both sulfadiazine and penicillin. Several of these cases in which operation was contemplated but deferred until the patients had been fortified with the antibiotic agents, resolved without recourse to surgery.

Ludwig's Angina is best treated by large doses of sulfadiazine and penicillin, with surgery at the optimum time.

Fulminating Laryngotracheobronchitis formerly carried an appalling mortality. Today the patient is placed in a humidified room in which the temperature is kept at 70° F and a hydrometer level of 100 is maintained. This saturation of the room atmosphere with moisture, combined with adequate treatment with penicillin, has greatly reduced the morbidity and mortality in this condition.

Patients undergoing such laryngeal operations as laryngotomy and laryngofissure have a much more speedy and tranquil convalescence if they receive chemotherapy during their hospitalization.

The prophylactic administration of either the sulfonamides or penicillin has greatly enlarged the field of labyrinthian surgery by minimizing the possibilities of suppurative labyrinthitis.

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DISEASES OF THE LUNGS DIFFERENTIAL DIAGNOSIS AND TREATMENT

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THIS subject is too broad to permit of detailed analysis in an article of this sort. It should be of help, however, to touch on the outstanding practical points in the diagnosis and treatment of certain diseases of the lung, even if such a dissertation does give away many of the trade secrets of the consultant in lung disease.

PULMONARY TUBERCULOSIS

No attempt will be made to describe this, the commonest of chronic lung diseases, but we must remind ourselves of its importance in the differential diagnosis of almost every lung disease and that signs of it occur most unexpectedly. Careful examination of the sputum for the presence of tubercle bacilli is too frequently omitted in the study of cases of lung disease in the general hospitals. Guinea-pig inoculation with sputum is often necessary for diagnosis.

In these days of mass x-ray study of the lungs of healthy people, so many shadows consistent with those produced by a tuberculous process are being found that there is present the constant necessity for deciding whether the patient should be treated as having early active but asymptomatic tuberculosis or whether he should be allowed to live a normal life and be followed by serial x-rays. In such cases the inoculation of fasting gastric contents into a guinea pig will surprisingly often prove that the infection is active.

Much will be said in the following discussion about bronchial obstruction and atelectasis. It is therefore timely to remark that all tuberculosis sanatoria are now cognizant of the frequency of tuberculosis of the bronchial mucosa which often results in bronchial obstruction and atelectasis. Usually there is evidence of tuberculosis in other parts of the lung, but occasionally a collapsed lobe is the only evidence of disease, and unless looked for the diagnosis of tuberculosis may be missed.

BRONCHIECTASIS

The classical symptoms of this disease are well known—cough with expectoration of large amounts of purulent, often foul, sputum. The typical case begins in childhood following an acute infection, particularly whooping cough, and very often it has led to early death from

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pneumonia or other complication directly attributable to the lung disease. It is usually found in the lower lobes, but often there is accompanying bronchiectasis in the right middle lobe or in the lingula of the left upper lobe which occupies much the same position on the left as the middle lobe on the right. These two portions of the lungs must be carefully studied in any case of bronchiectasis in which surgery is being considered. It must also be remembered that bronchiectasis can occur in an upper lobe alone. It is in such instances that an incorrect diagnosis of tuberculosis is frequently made. In upper lobe cases, and in all cases beginning in middle age, the bronchial infection and dilatation are often secondary to demonstrable partial bronchial obstruction from healed tuberculosis or benign tumor.

Hemorrhage, often large in amount, is fairly common and may recur frequently in association with the typical case of purulent bronchiectasis. Attention should however be called to an infrequent type of "dry" or "hemorrhagic" bronchiectasis in which sudden and profuse hemorrhage may be the first and only symptom. When the lobe of the lung of such a patient is examined after surgical removal the bronchial walls although dilated and therefore "bronchiectatic," may be abnormally thin and without gross infection, a condition contrasting sharply with that found in the ordinary case. The areas of bronchial dilatation in these patients may be small and not at the bases of the lungs where iodized oil is most easily placed.

Bronchiectasis, particularly in the lower lobes, can be diagnosed with a fair degree of accuracy in the plain x ray film. A lateral film is, however, necessary to show the commonly infected area behind the heart. A bronchogram with iodized oil is necessary in most cases, particularly in those being considered for surgery. At least one bronchoscopic examination should precede the bronchogram especially if the disease is localized in one lobe and there is any suspicion of bronchial obstruction with secondary bronchial infection.

It is surprising how often the sputum of a patient with bronchiectasis shows an almost pure culture of *Haemophilus influenzae*. The etiologic significance of this finding is unknown.

The pulmonary tissue outside the bronchial wall is often concomitantly infected causing multiple abscesses. This is particularly true when there is foul sputum.

Treatment—Until the past few years there has been no treatment that offered any hope of real alleviation of symptoms.

Most patients have found by experience that postural drainage in the morning and before going to bed at night gives varying degrees of relief for the persistent cough and expectoration. But this procedure never provides permanent relief. Bronchoscopic drainage has given temporary relief to many. Iodized oil treatment, x ray therapy and artificial pneumothorax have all failed.

The nasal accessory sinuses are frequently infected in association with the bronchial infection. Careful study should be made of this condition and rational treatment given, but cure of the bronchiectasis by this means cannot be expected. It should be remembered, too, that the sinuses can be infected from below by sputum coughed into the nasal passages.

Surgery is the great hope for the permanent relief of the distressing symptoms of bronchiectasis. With the development of thoracic surgery, cure of a large proportion of cases has been achieved. Before the war the operative mortality in lobectomy was reduced to about 3 per cent in the hands of the well trained surgeon. Now that we have penicillin, careful preoperative preparation with this substance has greatly improved the condition in which the patient comes to operation, and reduced the incidence of postoperative empyema. The operative mortality should now be even lower.

The recent reports of results with penicillin therapy have shown it to give more relief than would have been expected in view of the pathologic findings of the disease. There is little question that the amount of sputum is greatly reduced by the use of penicillin, but unfortunately the symptoms commonly return after the treatment is stopped. Much more study will be necessary to evaluate this form of therapy properly, and two questions in particular need to be answered: (1) Is "aerosol penicillin" by the inhalation method appreciably more effective than intramuscular injection? (2) In view of the multiplicity of organisms involved in bronchiectasis, as well as in lung abscess, should sulfadiazine be given with the penicillin? In any case there is now a promising method of treatment for patients whose disease is too extensive for surgical removal.

LUNG ABSCESS

This distressing and frequently fatal condition is still occurring both spontaneously and after various respiratory infections and operations on the nose, throat, lips and teeth. In hospitalized cases almost all studies until recently have shown a mortality of about 33 per cent, no matter what the treatment.

Lung abscess is diagnosed largely by the appearance of foul sputum with or without blood. Physical signs are notoriously absent or minimal. The x-ray usually shows a cavity, typically with a shifting fluid level, surrounded at first by an area of pneumonitis.

The x-ray diagnosis may be confused with tuberculosis, infected cyst, necrotic carcinoma, an abscess caused by Friedlander's bacillus, lymphoma with cavity formation, amebic abscess, pyopneumothorax and rarely diaphragmatic hernia. Occasionally an abscess gives a rounded shadow without cavity which may resemble a tumor.

In almost every case at least one bronchoscopy should be performed

to make certain that no foreign body tumor or other obstructing process is present in the bronchus

Treatment—Until the advent of penicillin more and more stress was being laid on early surgical treatment. One school urged one stage surgical drainage as soon as the diagnosis was made. By careful localization of the abscess its followers found that adhesions directly over the abscess allowed incision without the usual preliminary pleural pack to insure adherence of the lung to the chest wall. However, most thoracic surgeons advised a period of observation until about six weeks after the first symptoms of lung infection. In selected cases lobectomy was performed instead of incision and drainage. In many of the more chronic cases the best results are obtained by first draining the abscess and afterwards taking out the infected lobe. This latter procedure seems to be reducing the mortality rate appreciably for the type of abscess seen in the hospital.

In any case early hospitalization with postural drainage and probably bronchoscopy are urged. And now penicillin offers a promising form of medical treatment in the early stages. As in bronchiectasis the treatment is still on trial and again the addition of sulfadiazine may be wise. The colon bacillus is frequently found in the sputum along with a multitude of other organisms and in such cases sulfadiazine would seem particularly indicated.

BRONCHOGENIC CARCINOMA

This disease is being diagnosed with increasing frequency and should be considered in any questionable case of chronic lung disease particularly in the male of cancer age. The symptoms in order of frequency are cough, pain, weight loss, hemoptysis, dyspnea, fever and purulent sputum. Bloody sputum which persists day after day for weeks is almost always from cancer and not from tuberculosis or other disease.

From the standpoint of diagnosis it is fortunate that about 70 per cent of the cancers originate in the larger bronchi where the effects of bronchial obstruction are particularly evident and where the tumor can be seen through the bronchoscope and a biopsy specimen obtained. If the tumor is located more peripherally the correct diagnosis may be suspected because of the shape and density of the x-ray shadow. In a small group of cases exploratory operation offers the only means of diagnosis and it should not be postponed too long.

The physical signs of partial or complete bronchial obstruction are very helpful in the diagnosis. If there is a wheeze persistently localized to one area partial bronchial obstruction is almost certain, and the nature of the obstruction must be determined. Obstructive emphysema which can be demonstrated by films taken at full inspiration and full expiration is infrequently found in cancer cases. Complete atelectasis

of a lobe or segment of a lobe is a much more common finding, and in such a case the physical signs are dullness or flatness with absent breath sounds. These signs at the base of the lung are often due in part to the high diaphragm which has risen to take the place of the lung which was formerly expanded but has now, in the atelectatic state, been reduced in volume.

In about 25 per cent of all the cases metastasis to the lymph nodes in the neck will have taken place at the time of study, and a biopsy of such a node may establish the diagnosis. Careful palpation of the neck, particularly the region behind the clavicle, should be part of every chest examination. The trachea should likewise be palpated to see if displacement to one side, indicating bronchial obstruction with atelectasis, is present.

In a few cases in which other diagnostic methods have failed, cancer cells may be found in the sputum. If the cancer has spread to the pleura and there is pleural effusion, careful examination of the fluid will usually show neoplastic cells. It is occasionally helpful to remove fluid and replace by air in order to allow x-ray demonstration of pleural metastasis.

Treatment—As in cancer elsewhere, the only hope of cure is in early diagnosis and early surgical removal. To date the number of "five-year cures" is disappointingly low. It is to be hoped that the "total salvage" can be raised well above the 5 per cent rate that has previously been reported, but too great optimism is not justified.

Much time has been given to the differential study of the four types of bronchial carcinoma: the undifferentiated, the oat cell, the adenocarcinoma, and the epidermoid. On the whole the epidermoid type offers the most hope for surgical cure because in older people it may be slow growing. Recent surgical reports support this conclusion although early reports showed little difference in the results of operation on adenocarcinoma and the epidermoid type. The undifferentiated cell type occurs rarely and is rapidly fatal.

X-ray therapy is most helpful in relieving the symptoms of the oat cell type of growth. It is indicated in such cases, but offers no hope of cure and but little prolongation of life. X-ray therapy with the super-voltage equipment is used extensively in the treatment of the other types of bronchial cancer, but in the main has been disappointing. In certain cases it temporarily relieves bronchial obstruction and so improves the symptoms.

ADENOMA OF THE BRONCHUS

The possible presence of this so-called benign tumor of the bronchus should be kept in mind in all cases of atelectasis of a lobe or an entire lung. Sometimes the tumor itself casts an x-ray shadow visible within the lumen of the bronchus and sometimes its rounded surface is out

lined after lipiodol injection. Usually, however, the diagnosis is made by bronchoscopy in the attempt to explain atelectasis, bronchiectasis or abscess. If the bronchoscopist suspects tumor he should not be satisfied with one or even two or three reports of "chronic inflammation," but should try again to get a specimen from deep in the tumor mass.

These tumors bleed in almost every case, but the bleeding is intermittent rather than persistent as in carcinoma. Besides the hemoptysis the symptoms are usually those of suppuration in the collapsed lung beyond the obstruction. Sometimes an entire lung is destroyed in this process.

The treatment of this condition is usually lobectomy or pneumonectomy. Attempts at bronchoscopic removal are not very successful since the tumor is apt to develop outside as well as inside the bronchial wall. Sometimes, however, the adenoma is pedunculated and can be successfully removed piecemeal through the bronchoscope. A case is recorded in which the entire tumor mass was coughed out.

There are those who believe that these tumors should be considered potentially malignant.

PRIMARY PLEURISY WITH EFFUSION

Experience in the war has shown that too many physicians were not treating "primary" pleural effusions with the respect which is their due. Too often because the fluid disappeared in a few weeks and the x ray of the lung showed no underlying disease the effusion was regarded as a complication of "virus pneumonia" and the patient was returned to duty. A careful study in the Mediterranean Theater showed that a large pleural effusion was rare with "virus pneumonia" and that almost all the cases should be classified as subpleural tuberculosis with effusion. Follow up studies have shown that pulmonary tuberculosis seldom develops if the patient is given a rest period of about six months, and very frequently develops in about two years in patients not so treated.

In all cases of massive pleural effusion not shown to be due to the pneumococcus, streptococcus or other organism, the fluid should be carefully concentrated and the sediment injected into guinea pigs. Even if the guinea pig does not show tubercle bacilli the case should still be handled as tuberculosis. It should be remembered also that with proved tuberculous effusions the tuberculin skin test may diminish markedly in intensity or even be negative. In the past a negative tuberculin test in these cases has sometimes given a false sense of security.

While dealing with pleural effusions it should be noted that the signs of a considerable amount of fluid in the pleural cavity are not flatness with absent breath sounds as is frequently implied in the textbooks, but rather bronchial breathing which is usually distant, but may be intense, due to the fact that the fluid compresses the lung. A nasal quality of the spoken voice (egophony) is also characteristic of fluid.

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SPONTANEOUS PNEUMOTHORAX

The medical school teaching of thirty years ago was to the effect that spontaneous pneumothorax, like "primary" pleurisy with effusion, should be regarded as due to tuberculosis, and long periods of rest were prescribed. It is true that there may be a pleural tear due to underlying pulmonary tuberculosis, with resulting pneumothorax. But in practically all cases where there have been no previous lung symptoms, and the x-ray shows no lung disease, it has now been shown that the pneumothorax is due to the rupture of a bleb on the surface of the lung, and that in most cases the air is absorbed quite rapidly and there are no future difficulties. All patients are not so fortunate, and there may be several recurrences and even bilateral pneumothorax. It is doubtful, however, if long rest periods change the likelihood of recurrence.

The mechanism of the formation and rupture of the bleb is not well understood. In the past it was not uncommon to have a bus driver, for example, develop a severe chest pain while cranking his motor. When he came to the hospital pneumothorax would be shown on the x-ray. In many cases, however, the pneumothorax appears when the patient is sitting quietly or even reading in bed, or shortly after he gets up in the morning and is merely dressing.

In most cases a few days of quiet is all that is necessary, but it is important to watch the progress of the case and determine by x-ray film or fluoroscopic check whether the lung is reexpanding properly. Occasionally the lung shows no tendency to reexpand. In these cases it is usually safe and most effective to insert the needle of an aspirator between the ribs and actually suck out the air until the lung touches the needle. Even with a high positive-pressure pneumothorax the lung will usually stay out after such expansion. This plan of management is contrary to the teaching of the past, but has been proved successful by the experiences of Dr. L. F. Davenport at the Middlesex County Sanatorium.

In some cases the tear is so large or adhesions are holding it open in such a way that pneumothorax persists in spite of all "medical" efforts with a hollow needle, and surgical "interference" is necessary to close the leak.

Mention should also be made of the hemothorax which rarely accompanies spontaneous pneumothorax. If such a condition occurs the blood should be removed early since if allowed to remain it may organize and prevent reexpansion of the lung.

SARCOID AND SIMILAR DISEASES

Attention has lately been focused on a group of lesions with few symptoms but extensive x-ray changes which are being thrown into a diagnostic basket labeled "sarcoid." The disease was first described by

the dermatologists, but the diagnosis is now frequently made in cases which show no skin lesions. Comparatively benign bone lesions, eye changes (usually uveitis), or parotitis may form part of the syndrome. The spleen may be involved. In many of Longcope's cases among Negroes in Baltimore there was marked enlargement of the cervical nodes. For want of a better classification many cases with no demonstrable lesions outside the lungs are being diagnosed as "sarcoid." Usually the chest x rays show marked enlargement of the mediastinal

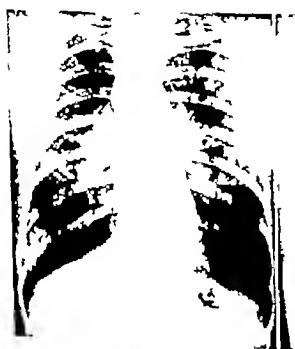


Fig 146



Fig. 147

Figs. 146 and 147—Sarcoid disease. This man was 28 years old. For two years he had had some night sweats and for three months fatigue. There was a little yellow sputum which was rarely streaked with blood. The tuberculin test was positive only with a 1:100 dilution of old tuberculin. Sputum was injected into a guinea pig, but no tubercle bacilli were demonstrated. Bronchoscopy and bronchography were negative.

A diagnosis of sarcoid disease was made on the basis of the x ray findings of characteristic enlarged nodes in the right upper mediastinum and below the right lung root and scattered areas of density in both lungs (Fig 146) as well as the weakly positive tuberculin test.

In ten months the lungs were clear (Fig 147).

nodes, notably those below the hilum and accompanying changes in the lung which look somewhat like patches of fibrosis. An incorrect diagnosis of lymphoma is frequently made. In most instances the lesions disappear with or without rest, in a period averaging two years. The most confusing cases are those in which at a certain stage the x ray shows the disappearance of the shadows of the mediastinal glands and only a picture of military disease in the lungs indistinguishable from military tuberculosis.

Not all cases are essentially asymptomatic. Marked weakness or

cough or fever may be present. In rare cases the bronchi are partially obstructed by tissue which on bronchoscopic biopsy the pathologist calls "sarcoid."

There has been much discussion as to the nature of this disease. Histologically the appearance is that of noncaseating tuberculosis. Many have therefore maintained that it is a form of tuberculosis. Strangely enough the tuberculin test, using a strength of 1:100 Old Tuberculin, is usually negative. Such a negative test is considered important in diagnosis, but a weakly positive test is not considered sufficient to rule out the diagnosis of sarcoid disease. Biopsy of a skin lesion or an enlarged node may be of help.

It is not desired to place too much emphasis on a comparatively rare disease, but it is important to know of this condition which shows extensive x-ray changes, but usually runs a rather benign course.

In this connection mention should be made of another condition that is regarded by many as a manifestation of tuberculosis, namely *erythema nodosum*. In it the chest x-ray often shows enlargement of the mediastinal glands in the same location as in the sarcoid cases. In addition there are sometimes changes in the lung tissue with a linear or miliary appearance.

It may be worth while at this point to enumerate the unusual conditions in which the x-ray shows a miliary process. Such shadows may appear in miliary carcinoma (originating in the lungs or outside the chest), bronchiolitis fibrosa obliterans, acute bronchiolitis, yeast and fungus infections, tularemia, psittacosis and periarthritis nodosa. They may be present also in certain industrial diseases, notably those of some workers in fluorescent lamp factories, hematite miners, welders who work in enclosed spaces, workers in cotton and sugar industries, and in the early stages of silicosis.

PULMONARY INFARCTS

In these days when so much attention is paid to peripheral vascular disease, particularly thrombophlebitis or phlebothrombosis, and the femoral veins are so commonly ligated in order to prevent emboli to the lungs, it is especially important to look for pulmonary infarction. It is equally important that the diagnosis of infarct be on a sound basis, since veins are often ligated when the diagnosis of infarct is made, even if the legs show little or no evidence of venous involvement.

The classical symptoms of infarct are pleural pain, the expectoration of bloody mucus or blood, and the development of a friction rub. Dyspnea and orthopnea may be present. But the characteristic symptoms are often lacking and there may be only short periods of dyspnea or fainting. The temperature, pulse and respiration are frequently, but by no means always, all elevated. With a large infarct the temperature may be as high as 103° F. even though infection cannot be shown.

The whole picture may easily be confused with pneumonia. Fluid, which is commonly bloody often develops in the pleural cavity and a chest tap may be a useful diagnostic measure.

Hampton and Castleman have pointed out that there are two varieties of infarct, the true and the incomplete. True infarcts are those in which there is tissue necrosis with destruction of the alveolar walls, and later healing with the formation of scar tissue. Experimentally and

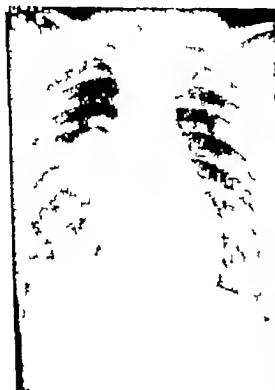


Fig. 148



Fig. 149

Figs. 148 and 149—Incomplete infarct. The patient was a woman of 20. She had an incomplete miscarriage of a blighted ovum. The following day a curettage was performed under gas-oxygen anesthesia. Two days after the operation there was a slight cough and a temperature of 101° F. Three days after the operation the temperature was 103° F and the pulse 110. There were a few rales in the right back. No hemoptysis occurred. On this day the chest film (Fig. 148) showed a 6 cm. area of density located opposite the right lung root. Two days later there was marked clearing (Fig. 149). In four days the shadow had completely disappeared. The x-ray and clinical evidence in this case are more suggestive of infarct than of pneumonia, but a true infarct would not have cleared as quickly.

Clinically such infarcts develop only when there is some blocking in the return of the pulmonary venous blood to the heart. Congestive heart failure and interference with the muscles of respiration provide such blocking and it is not strange that true infarcts occur in two clinical conditions: heart disease and after operation particularly for serious disease. With an incomplete infarct there is engorgement of the pulmonary vessels with alveolar hemorrhage, but some air is retained in the infarcted area. The symptoms are usually less severe than with true

infarct Because of partial aeration, the x-ray shadow is less dense and it may completely disappear in two to four days True infarcts vanish much more slowly, and usually leave a horizontal linear scar

It was formerly held that a pulmonary infarct must cast a shadow triangular in shape with the apex toward the heart, but Hampton and Castleman made very careful postmortem studies and proved that infarcts are almost never pyramidal in shape but, being located at the periphery of the lung, usually where two pleural surfaces meet, they simply take the shape of that portion of the lung which is involved The border of the infarct toward the heart tends to be convex

Even with this knowledge about infarcts the diagnosis is often difficult It should be suspected in any pulmonary condition which occurs in heart disease, or in pulmonary complications occurring from one to three weeks after operation It may occur also in any case of disease of the veins, in debilitating medical conditions, and rarely after a minor injury such as a sprained ankle

IDIOPATHIC PULMONARY FIBROSIS

In cases of dyspnea with or without chronic bronchial infection the x-ray may show extensive fibrosis of the lungs In such conditions blebs are often present and are best shown under the sternum in the lateral x-ray Sometimes these cases may be "burned out tuberculosis," and rarely tubercle bacilli are found after repeated search After careful study most of the cases have to be classed as idiopathic fibrosis Occasionally the condition develops relentlessly over a period of months with increasing dyspnea Some of these patients are the "chronic asthmatics," and some have repeated attacks of "pneumonia" with organization and permanent scarring Right-sided heart failure or true cor pulmonale may develop

Treatment is very difficult and consists largely of alleviation of symptoms as they arise One tries to eliminate foci of infection, usually without much change in symptoms If arrangements can be made, winters are best spent in a warm climate

TUMORS OF THE LUNG

It is impossible to give more than passing notice to tumors of the lung other than those already mentioned "Benign" tumors occur in great variety, but many are potentially malignant The commoner forms are simple cysts, neuromas, teratomas, and a group of connective tissue tumors (chondromas, fibromas, and so forth)

The ganglioneuromas and neurofibromas are potentially malignant and as a rule develop from the sympathetic chain They are therefore usually located posteriorly in the chest and close to the mediastinum Their borders are apt to be sharply defined Often they cause changes in the vertebrae or spreading of the ribs

Teratomas including the so-called dermoid cysts commonly arise from one or many germ layers near the anterior chest wall on either side of the mediastinum. The x ray may show fragments of bone or teeth, and rarely the patients coughs up hair.

The differential diagnosis of lung tumors must take into account substernal thyroid, aneurysm, dilated esophagus or tumors of the esophagus itself, mediastinal abscess, tumors of the chest wall, echinococcus cyst, and a conglomeration of tubercles which assumes a sharply defined spherical shape and is commonly called a tuberculoma.

Many of these tumors are best removed surgically.

MISCELLANEOUS CONDITIONS

In the Boston area yeast and fungus infections are considered unusual, but we may be missing certain cases. Cases of moniliasis and aspergillosis are found. They have usually yielded to treatment with iodides.

Actinomycosis of the lung is uncommon but may occur even when no explainable source of infection is present, as in certain women. Where a chest wall abscess develops after a lung infection, actinomycosis is almost always found to be the cause. Surgical drainage and excision are still considered necessary but are accompanied by prolonged treatment with sulfonamides or penicillin. There have been some cures.

Because of the number of cardiac patients sent to tuberculosis clinics as a result of x ray changes in the lungs it is worth while to call attention to the fact that pulmonary congestion and edema may give shadows not limited to the lung roots or bases. Where heart disease is known to be present edema limited to the lungs must be looked for as well as pulmonary infarction which has already been mentioned.

OFFICE LABORATORY TESTS

Technic and Interpretation

MALCOLM M. STANLEY, M.D.^{*}

THE following laboratory tests were chosen for discussion because of their ready applicability to clinical problems frequently encountered by the practitioner, and because they can be done in the office, for the most part with a minimum of expensive or complicated equipment.

URINE

I Bile in the Urine.—Although commonly occurring in the urine in conjunction with bile salts and other components of bile, bilirubin is usually tested for because of its relative ease of detection. The presence of bilirubinuria indicates that there has been a "regurgitation" of bile already formed by the liver into the blood stream from which it was excreted by the kidneys into the urine. This regurgitation may occur following necrosis of the liver cells as a result of infection ("infectious hepatitis"), the action of toxic substances such as arsenic ("toxic hepatitis"), or the effect of back pressure because of obstruction of some portion of the biliary system ("obstructive jaundice"). In uncomplicated hemolytic icterus there is no bile in the urine. Hence, in an icteric patient this determination is of value in narrowing the possibilities as to the causative mechanism. Bilirubinuria in small amounts may be the earliest detectable sign in infectious hepatitis and should be searched for in obscure febrile illnesses of short duration with vague abdominal symptoms, particularly with a history of exposure, in order that the disease be diagnosed in its incipient (preicteric) stage. Routine tests at short intervals of the urines of industrial workers exposed to hepatotoxic agents have been of value in detecting those with early liver damage in order that they might be removed from the deleterious environment before serious harm had taken place.²

TESTS

I "FOAM" TEST

A test tube half full of the urine is shaken vigorously, holding the thumb over the open end. The color of the layer of foam which forms on top of the urine is compared against a white background with a normal

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urine treated in the same manner. If the foam is yellow the test is positive. It is to be emphasized that slight discoloration of the foam, indicating a small amount of bile, can be detected only by comparison with a normal control.

The foam test is a most sensitive method for detection of bile, and is the most easily performed of all. Its only disadvantage is that the presence of substances such as penicillin, streptomycin, phenolsulfonphthalein in acid solution, riboflavin, atabrine and possibly others (not, however, urochrome) will cause a false positive. Its interpretation is difficult when patients are receiving these drugs, so other confirmatory determinations must be made in those instances.

2. METHYLENE BLUE TEST⁷⁻⁹

A 0.2 per cent aqueous solution of methylene blue chloride is added drop by drop (using a pipette which delivers 20 drops of the solution per cubic centimeter) to 5 cc. of a prebreakfast urine specimen. The reading (in drops) is taken as one less than the number needed to change the color from green to blue. If more than 8 drops are required a smaller measured amount of urine is diluted to 5 cc. with distilled water and the test repeated in order that a clearer end point may be obtained. If diluted, the number of drops is multiplied by the dilution factor. A reading greater than 4 drops has been regarded (by Cellis and Stokes, et al.) as a positive test for bilirubin in the urine. Readings of 2 to 4 drops inclusive have been regarded as suggestive and as an indication for additional studies.

As Myers² described the test, 2 drops of methylene blue solution were added to 10 cc. of urine. The solution remains dark blue if negative but turns a brilliant green if positive for bile. He quantitated the test by progressively diluting the urine, keeping the total volume at 10 cc. by replacing increasing amounts of urine with distilled water until a negative result was obtained.

Frankel introduced the methylene blue test in 1931.⁸ This soon brought forth several communications in protest⁴ and approval,^{5, 6} just as did Myers' recent paper.⁷⁻¹¹ The majority of these authors state that a positive test results from the simple mixing of the two colors blue and yellow and not from the oxidation of yellow bilirubin to green biliverdin with conversion of the methylene blue to the colorless leuko form as was Frankel's original belief. The consensus and bulk of the evidence indicate that the blending of colors accounts for most of the green color phenomenon.

Because a positive test results from blending of the yellow and blue colors, false positives are also likely to occur when other pigments are present in the urine as in the foam test. Its most ardent advocates^{7, 8} admit its inferiority in sensitivity and specificity to the Harrison and diazo spot test. On the other hand, it is performed in a roughly quantitative manner and may be of value in following the course of patients with parenchymal liver disease such as infectious hepatitis, since the

titer diminishes and the test becomes negative during convalescence when the icterus is still present and the serum bilirubin is still elevated

3 DIAZO SPOT (Godfried¹)

Five cubic centimeters of 10 per cent barium chloride and 10 cc. of urine are mixed and the voluminous precipitate of insoluble barium salts is filtered. The wet filter is placed on a disk of dry filter paper so that the excess liquid is removed. To the precipitate on filter paper add 1 drop of Ehrlich's diazo reagent, 4 drops of 95 per cent alcohol, and 1 drop of phosphate buffer (6 per cent $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$). A red to pink color indicates a positive reaction. If there are large amounts of bilirubin, the test works better when the urine is diluted.

(*Ehrlich's Diazo Reagent* This is a mixture of two solutions, each of which keeps well, but which must be freshly mixed immediately prior to using. *Solution 1* Sulphanilic acid, 5 gm., concentrated hydrochloric acid, 50 cc., distilled water to make 1000 cc. *Solution 2* Sodium nitrite, 0.5 gm., distilled water, 100 cc. Take 0.8 cc. of solution 2 and make up to 25 cc. with solution 1.)

4 HARRISON SPOT (Godfried¹²)

Precipitate the bilirubin with barium chloride and filter as in the Diazo test (3 above). To the precipitate on filter paper 1-2 drops of Fouchet's reagent (25 per cent trichloroacetic acid containing 0.9 per cent ferric chloride) are added. If bilirubin is present, the characteristic blue to green color appears.

When the barium chloride and urine are mixed the barium ions and sulfate ions present in the urine form insoluble barium sulfate which precipitates. The bilirubin is adsorbed onto the barium sulfate particles, hence, is "concentrated." The blue to green color of a positive Harrison test is the result of oxidation of the adsorbed yellow bilirubin to biliverdin or bilocyanin. Both the Harrison and the diazo spot tests are "concentration" tests.

Both the Harrison spot and diazo spot tests are very sensitive and quite specific. Their only drawback is that they are more complicated and require more time and equipment. According to Godfried,¹² 0.002-0.008 mg. of bilirubin per 100 cc. of urine is detectable by these methods.

5 HARRISON MODIFICATION (Hawkinson, Watson, and Turner¹³)

a. *Preparation of Barium Impregnated Paper Strips*—Pieces of extra thick and retentive filter paper are allowed to remain briefly in a saturated aqueous solution of barium chloride (Schleicher and Schull number 470 filter paper is recommended. Lighter grades are not satisfactory. We have found that ordinary unglazed heavy white blotting paper is quite adequate.) They are then dried in the air or, preferably, in a drying oven, after which they are cut into strips 4 inches long by $\frac{1}{2}$ inch wide.

b. *Procedure*—One end of a barium chloride impregnated strip is placed in the urine sample to be tested, the strip being in an approximately vertical position, at least one half extending above the surface of

the sample. After standing in the urine for from thirty seconds up to two minutes the strip is withdrawn and placed on a piece of dry paper such as a paper towel or any other absorbent paper. Inspection of the filter strip will usually reveal somewhat more color in that area which corresponded to the surface of the urine. Two to three drops of Fouchet's reagent (see above) are then dropped directly on this area. A positive test is denoted by the appearance of a green color varying in intensity with the amount of bilirubin present. With smaller amounts the color is often detected as a faint green line running across the strip.

The urine to be tested may be agitated by shaking, by bubbling air through the liquid, or by forcefully drawing it up and squirting it back from a syringe into a beaker several times so that there is a layer of foam on the surface. If the barium chloride impregnated strip is then inserted into the liquid through the layer of foam, and the test carried out other wise as described above we have noted that its sensitivity is markedly increased. In effect, this combines the principles of the foam test and the Harrison test.

Hawkinson, Watson, and Turner consider that their modification is just as sensitive as the original Harrison test. This has been our experience with the procedure. The modification of the original Harrison technic is "especially suited for mass and serial usage" and would seem to have eliminated all the objections to the original method while retaining its advantages of sensitivity and specificity. It is easily and quickly performed and requires, besides the barium chloride impregnated strips, only one reagent which will keep indefinitely.

Because of its extreme simplicity it would seem that the foam test is useful as a screening test which should be done on all urines as a part of the routine urinalysis. Confirmation of a positive foam test if necessary can be obtained with one of the more specific procedures. For this the modified Harrison test is recommended because of the ease and speed with which it can be performed.

II. Glycosuria.—The importance of testing the urine routinely for sugar is now too well recognized to require emphasis. The discovery of glycosuria during the course of a routine "check up" particularly of the members of the family of a diabetic, is often the first evidence of diabetes. It may occur long before obvious symptoms make their appearance. Adherence to the custom of determining urine and blood sugars while the patient is in the fasting state when diabetes is suspected may, however, result in unnecessary delay in diagnosis.¹⁶ In the mild diabetic the urine may be free from sugar and the blood sugar may be normal in the fasting state, particularly before breakfast after a ten to twelve hours fast. Therefore, in patients who are suspected of having diabetes these tests should be performed on specimens taken two to four hours after a meal heavy in carbohydrate, or a glucose tolerance test should be done. Do not do single fasting blood and urine sugars when the object is to establish the diagnosis of diabetes in a doubtful case.

1 QUANTITATIVE ESTIMATIONS OF URINARY GLUCOSE

The necessity for basing the determination of adequacy of control of diabetics on the *quantitative* estimation of sugar spilled in the urine during the twenty-four-hour period, rather than on qualitative tests on periodic specimens, has recently been reiterated.¹⁷ Especially when controlled on protamine zinc insulin alone are diabetics liable to spill small amounts of sugar after meals. When the total for twenty-four hours is measured, the amount is often found to be insignificant. It has been our goal to control patients in the clinic so that 5 gm of glucose or less are lost in the urine per day.

A. MODIFIED BENEDICT METHOD¹⁸

To 2.5 cc of reagent in a pyrex test tube add approximately 1 gm of anhydrous sodium carbonate. Heat slowly to boiling over a low flame. Add the urine slowly, drop by drop, from a pipette graduated in tenths of a cubic centimeter, while the solution is kept boiling. The end point is complete absence of blue color. The white precipitate of cuprous thiocyanate by contrast makes the end point easier to determine.

If x is the number of cc of urine required for reduction, the formula for computing the percentage of glucose is as follows:

$$\frac{0.005}{x} \times 100 = \text{percentage of sugar}$$

If there is a high concentration of glucose, it may be advantageous to dilute the urine 1:10, in which case the formula is

$$\frac{0.005}{x} \times 1000 = \text{percentage of sugar (in original urine)}$$

The reagent (25 cc are reduced by 5 mg glucose) is composed of the following (only the copper sulfate need be weighed accurately)

Copper sulfate (pure crystallized)	18.0 gm
Sodium carbonate (crystallized)	200.0 gm
or Anhydrous sodium carbonate	100.0 gm
Sodium or potassium citrate, C.P.	200.0 gm
Potassium thiocyanate, C.P.	125.0 gm
Potassium ferrocyanide solution (5 per cent)	50 cc.
Distilled water, to make	1000.0 cc

With the aid of heat dissolve the carbonate, citrate and thiocyanate in about 700 cc of water and filter. Dissolve the copper sulfate in 100 cc. of water and pour slowly into the other fluid, stirring constantly. Add the ferrocyanide solution, cool and dilute to 1000 cc.

This reagent may also be purchased already prepared from many pharmaceutical firms.

2. METHODS BY WHICH DIABETIC PATIENTS THEMSELVES CAN DETECT GLYCOSURIA

Every well trained diabetic should learn how to test his own urine for sugar and ketones, and should perform at least the former test every day. There are several different outfits which are available for these procedures

A. BENEDICT QUALITATIVE TEST"

Eight drops of urine are added to 5 cc (approximately 1 teaspoonful) of Benedict's qualitative solution and thoroughly mixed by shaking. The test tube is placed in *boiling* water for five minutes. The amount of sugar is estimated by the degree of reduction, from green to red.

The reagent contains copper sulfate, sodium or potassium citrate and sodium carbonate. The reaction is the familiar one of reduction by glucose of the cupric salt to cuprous hydrate (yellow) or cuprous oxide (red). A pint of solution (enough for approximately 100 tests) costs from 59 cents to \$1.00. Two test tubes and a medicine dropper cost an additional 25 cents. Each test, therefore, costs less than 1 cent.

This procedure is quite satisfactory when performed by the patient or physician according to directions. It is the least expensive. However the variations in results are amazing when the reagent, the urine, or both are not measured, or the boiling is inadequate. The test requires several minutes and the equipment is bulky and difficult to carry on one's person. An external source of heat is necessary. Because of these inconveniences particularly during vacations when traveling or visiting, patients often neglect this procedure entirely. When dietary indiscretions common to such periods occur, derangement of control may be serious without the patient's knowledge.

B. "CLINITEST" TABLET METHOD"

This set is packed in a small plastic case (8 by 5 by 3.5 cm) which fits into the pocket or purse and which contains all the necessary materials (dropper, test tube and bottle of 36 reagent tablets). The top of the case is designed for collection of the urine specimen. The retail price of the kit is \$1.75 (includes 36 tablets). Additional tablets are 60 cents for 36. Each test costs approximately 17 cents, disregarding the initial cost of the kit.

Twenty-five one hundredths milliliter (5 drops) of urine is added to 0.5 ml. (10 drops) of water in the small test tube and one reagent tablet is dropped into this solution. A boiling reaction occurs immediately and if glucose is present a colored precipitate of cuprous oxide will form. The degree of reduction is estimated as in the Benedict qualitative test. A color scale for comparison is part of the kit.

The components of the reagent tablet are essentially the same as in the Benedict solution except for the presence of sodium hydroxide, citric acid and sodium bicarbonate instead of sodium carbonate and sodium citrate. However, upon being dissolved the tablet produces sodium citrate, carbon dioxide and a very small quantity of sodium bicarbonate. In addition, the heat resulting from the ionization of the solid caustic and the neutralization between sodium hydroxide and citric acid is sufficient for the reduction of the cupric ions in the presence of glucose.

Recently, testing of several thousand diabetic urines by trained laboratory technicians, using both the Benedict qualitative and the Clinint methods, has shown agreement in 84 per cent of the specimens.¹⁹

As the test can be done in less than a minute and requires no external source of heat, it is of great value to patients who are traveling, staying at hotels, and the like. This set combines the virtues of simplicity, convenience, portability and inexpensiveness and is the best outfit available for the purpose.

C "SHEFTEL" TABLET METHOD²⁰

This urine sugar test case is a somewhat elaborate outfit in a 12 by 11 by 3.7 cm plastic box. The box opens so that the top forms a rack which holds (1) the test tube in position for heating, (2) two vials, one containing 60 copper sulfate reagent tablets and the other 40 methenamine tablets which are burned for a source of heat, (3) a graduated dropper-pipette, and (4) a combination glass spoon and rubber test tube cleaner. A color scale and durable book of instructions are also provided. The retail price is \$3.75, including the above reagent and fuel tablets. Each test costs 2½ cents, disregarding the initial cost of the outfit.

To 1.5 cc. of water in the test tube are added 0.25 cc. of urine and a copper sulfate reagent tablet. A methenamine tablet is placed on the metal well just below the bottom of the test tube, and lighted. The fuel tablet burns for 2¼ minutes, boiling the solution and carrying the reduction reaction to completion.

The reagent tablet employs the same chemicals that are used for the Benedict qualitative test, namely copper sulfate, sodium or potassium citrate, and sodium carbonate, but with the addition of acacia and creatinine. The big disadvantage is that an external source of heat is required. Both the initial cost and the cost of each test are relatively high. The case is slightly large to be carried conveniently in the pocket. A separate container must be provided for the urine to be tested. On the other hand, the procedure may be done precisely and in a roughly quantitative manner. The case is sturdily constructed and quite durable.

D "GALATEST" POWDER METHOD

This "outfit" is composed of two tubes of dry reagent powder (one for testing for sugar and the other for acetone) and a medicine dropper contained in a flimsy unpainted wooden box 10 7 by 6 by 3 cm (1) The white "Galatest" powder (for sugar detection) is a mixture of bismuth oxychloride, sodium hydroxide and sodium silicate (2) The "Denco" powder (for acetone detection) is a mixture of sodium carbonate, ammonium sulfate and sodium nitroprusside. The cost of the set is \$2.25, or \$1 00 for each of the tubes of powder. Each tube contains material for approximately 100 tests, so the cost is about 1 cent each.

Deposit on a piece of plain white paper a little of the "Galatest" powder (covering an area about the size of the little finger nail) Use dropper and deposit 1 small drop of urine on the powder. The presence of sugar is indicated by a change in the color of the powder ranging from gray-green to black, depending upon the amount.

In this instance the glucose reduces the bismuth oxychloride to black bismuth oxide in the cold. It is easily portable, and the procedure is very simple to perform. Again, however a separate container must be provided for collection of the urine. The colors are not as sharply defined as in the more familiar copper reduction tests, and a maximum of 1 per cent glucose in undiluted urine can be detected.

(To detect acetone the above procedure is followed, using instead "Denco" powder and 2 to 3 drops of urine. A positive test is indicated by color changes ranging from light lavender to dark purple and requires about one minute for completion. If no acetone is present, the powder will take on a grayish yellow color.)

STOOL

Every patient who enters the hospital or who undergoes a physical examination as a periodic routine procedure or for other reasons should have a stool examination, for occult blood at least. Occult blood in the stools is confirmatory evidence in many cases of malignancy of the stomach or large bowel or active peptic ulcer. A persistently positive test may provide the reason for an obscure anemia or diarrhea.

An adequate specimen can be obtained on the gloved finger at the time the digital rectal examination is made. Only rarely must this procedure be postponed because of an insufficient amount of feces in the rectum. Unfortunately examination of the stool, although it may often be diagnostic, is the most frequently neglected laboratory test.

CLINICAL TESTS FOR OCCULT BLOOD

1. TECHNIC FOR GUAIC TEST

Place a small amount of material (feces, gastric contents) in a depression on a white spot plate (tile) and mix with several drops of glacial

acetic acid. Add 2 or 3 drops of gum guaiac solution and mix again. Add 2 or 3 drops of 3 per cent hydrogen peroxide. Development of a green or blue color is a positive reaction. The rapidity with which the color develops and the depth of color are some indications of the amount of hemoglobin present.

REAGENTS (should be kept in dark bottles, as they are decomposed by light) —
 1 *Gum guaiac* 1 gm of gum guaiac in 60 cc of 95 per cent alcohol or in 60 cc. glacial acetic acid
 2 *Hydrogen peroxide* 3 per cent aqueous solution. Keep refrigerated if possible. (In case of a negative result, it is well to perform the test on a small amount of blood if there is any doubt as to the potency of the reagents particularly the hydrogen peroxide.)

2 TECHNIC FOR BENZIDINE TEST

A saturated solution of "benzidine base for blood detection" in glacial acetic acid is used instead of the gum guaiac solution. The test is otherwise performed in the same way as the guaiac on the stool.

Blood and certain other substances contain the enzyme peroxidase which catalyzes the oxidation of the base compound (guaiacol or benzidine base) to a green or blue colored complex. An excess of hydrogen peroxide rapidly destroys this colored complex and also oxidizes and destroys hemoglobin. Therefore, hydrogen peroxide must not be added in excess and must be added after the guaiac or benzidine solution.

Factors Influencing the Tests and Their Interpretation—Feces contain substances which inhibit the peroxidase reaction. Bramkamp²³ found that when hemoglobin was mixed with the feces, five times as much was needed to produce a positive benzidine reaction as was necessary when it was in watery solution. A concentration of 0.04 per cent blood freshly mixed with the stool will cause a positive benzidine test. The ingestion of 1.5 to 2 gm of hemoglobin (9.4 to 12.5 cc of blood containing 16 gm of hemoglobin per 100 cc) over a day's time resulted in positive tests in only 35 to 48.5 per cent of the normal subjects, however.²⁴ Pancreatic digestion is probably largely responsible for this variable loss of ability to reduce peroxides which occurs on passage of blood through the intestines,²³ although other factors such as intestinal motility may influence it.²⁴ Thus, when blood is taken by mouth, ninety times as much may be required to produce a positive test as when the blood is freshly mixed with the stool. Hence when the site of bleeding is in the esophagus, stomach or duodenum, relatively large amounts of blood must be lost before it can be detected by the usual tests. In contrast to this, as little as 0.04 per cent blood theoretically will produce a positive reaction when the source of bleeding is in the large bowel.

The benzidine reaction will often be positive on the stools of normal persons if their diets contain meat. The guaiac test is somewhat less sensitive, hence it is not necessary to have the patient on a meat-free

diet, particularly if only a blue or strong blue-green color is regarded as positive, and not the lighter shades of green. It is for this reason that we routinely employ the guaiac test, realizing, however, that it is not as sensitive as the benzidine test, and that it will not detect small hemorrhages.

In testing for hemoglobin in the urine, the extreme sensitivity of the benzidine test is a virtue and makes it preferable to the guaiac test in this instance.

False Positives—A number of other substances will produce the green or blue color reaction besides hemoglobin. The common ones are milk, pus, ferrous sulfate, bromides, iodides, and copper compounds (such as the copper precipitate left on the walls of test tubes after Benedict's test for sugar). Usually administration of ferrous iron by mouth, although causing the stool to appear "tarry," will not produce a strongly positive guaiac reaction. This is because the unabsorbed iron is either found "in firm organic combination"²⁰ after its passage through the gut, in which nonionized form it will not catalyze the reaction, or it is oxidized to the ferric state soon after defecation, when exposed to air. In rare instances, however, iron therapy will cause a false positive guaiac test, apparently because some of the ferrous form appears in the feces unchanged. We have seen at least one case in which there was good evidence that ferrous sulfate caused a false positive guaiac test on the stool.

From consideration of the above facts it may be seen that a negative test for fecal occult blood does not rule out small amounts of bleeding, particularly if it occurs high in the gastrointestinal tract, neither does a positive test necessarily indicate that the stool contains blood. Despite these limitations the procedure is an extremely valuable one and should be performed routinely in the office and clinic as well as in the hospital.

ERYTHROCYTE SEDIMENTATION RATE

In the presence of inflammation and tissue destruction of any sort, there are various nonspecific responses among the more important of which is an increased production of plasma fibrinogen in the liver.²¹ The rate of sedimentation of the red cells has been observed to parallel these increases in blood fibrinogen.²² Thus, it is elevated in acute and chronic infectious diseases, malignant neoplasms, leukemia and lymphoma, acute and chronic nephritis in the active stage, coronary thrombosis and thromboses in general. It is also elevated in normal and abnormal pregnancy, and during the menstrual flow. It is usually depressed in severe cardiac decompensation, presumably because of interference with hepatic function. It may also be decreased in various forms of severe liver disease, especially in the chronic stages such as cirrhosis of the liver. It is not altered by fever itself such as produced by the hyperthermia but it is often elevated in the presence of fever, in

which cases it is presumed that both the fever and the elevated erythrocyte sedimentation rate represent responses to an underlying inflammatory process

The erythrocyte sedimentation rate is often advantageously used as an aid in determining the progress and treatment of certain chronic infections, such as rheumatic fever, tuberculosis and arthritis. It should be emphasized that it is entirely a nonspecific test,^{29, 30} and hence is of no diagnostic value beyond that of a simple indication of the presence, and presumably the amount, of inflammatory reaction.

Two of the several technics available appear to be quite satisfactory.²⁸ One, the Westergren method,³¹ is quite simple to perform and produces reliable results in most instances. In the presence of severe anemia, however, it may be inaccurate. In such instances the Rourke-Ernstene³² method may be preferable, although for routine use the increased time and effort required for its performance makes it less satisfactory than the Westergren method.

TECHNIC OF THE WESTERGREN METHOD

Draw venous blood without stasis. Add exactly 3 cc. of blood to 0.75 cc. of 3.8 per cent sodium citrate solution in a calibrated tube. It is better to use a tube such as the ordinary calibrated centrifuge tube rather than depending upon the calibrations of the syringe to measure the desired quantity. Mix the blood and draw into Westergren tube to the height of 200 mm. (to the zero mark.) Determine the distance of fall of the erythrocyte column (the distance between the meniscus and the line of demarcation between the red cell layer and plasma) at the end of exactly one hour.

The normal values for the erythrocyte sedimentation rate by this method are 1 to 7 mm. per hour for men and 4 to 11 mm. per hour for women and children. The values above 15 mm. per hour are abnormal. Values of from 12 to 15 mm. per hour are of questionable significance.

TECHNIC FOR THE ROURKE-ERNSTENE METHOD

Draw venous blood without stasis. Place 5 cc. in a bottle with dry oxalate mixture (4 mg. of potassium oxalate and 6 mg. of ammonium oxalate—Heller and Paul³³). Fill the Wintrobe tube to "10" mark (100 mm.). The level of the red cell layer is read each five minutes for one hour.

Uncorrected Sedimentation Rate—Add the millimeters of sedimentation in the two fastest five minute periods and divide the sum by ten. This gives the most rapid rate of fall in millimeters per minute.

Hematocrit (percentage of packed cells)—Centrifuge the tube for one hour at 3,000 R.P.M. and read the percentage erythrocytes.

$$\text{Per cent cells} = \frac{\text{height of packed erythrocytes}}{\text{total height of column of cells and plasma}} \times 100$$

"Corrected Sedimentation Rate"—Derive the "Corrected Sedimentation Rate" from the uncorrected sedimentation rate and the hematocrit using the reference chart of Rourke and Ernstene.³²

Special Precautions for Performing Sedimentation Rate by Either Technic—1 Always use the proper anticoagulant for the technic performed.

2. Perform the test as soon as possible after taking the sample. If blood stands more than two hours, the sedimentation rate is slowed and the test is valueless

3 Be certain that the tube is exactly vertical. An inclination of only 2 per cent may accelerate settling velocity by 30 per cent.

4. Wide fluctuations of temperature influence the rate of sedimentation.

5 Any tendency of the blood sample to clot and any gross hemolysis invalidates the result

Determination of the erythrocyte sedimentation rate, particularly the Westergren type, is such a simple procedure that it can readily be done in the office. The necessary apparatus, racks and tubes are quite inexpensive.

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CLINICOPATHOLOGIC CONFERENCE

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REPORT OF THE CASE

A 45 year old unmarried carpenter of Swedish extraction entered the hospital because of aching and swelling of both ankles of sixteen months duration

Family History and Past History were entirely negative.

Present Illness began sixteen months before admission when the patient injured both ankles in a fall. Although no fracture was present he thereafter noted intermittent swelling and aching of the ankles, increasing through the day, and subsiding overnight. These symptoms prevented his return to work after the accident. Two weeks prior to admission the swelling spread so as to involve the legs, thighs, abdomen, hands and face. For six days before admission he experienced dryness of the throat, hoarseness and slight rhinitis. There was no hemoptysis, cough, expectoration, dyspnea, palpitation, chest pain, nausea or vomiting. Nocturia was noted but no hematuria, frequency or dysuria occurred. The patient lost 5 pounds in the two weeks preceding admission.

Physical Examination revealed evident weight loss, marked respiratory difficulty, a grossly audible expiratory wheeze, edema of the right eyelid, face, right hand and arm, cyanosis of the ears, lips and fingers, and slight distention of the neck veins. The right side of the chest was depressed and respiratory excursion was diminished over the entire right side anteriorly. Flatness and decreased breath sounds were noted in the right axilla and right lower lobe posteriorly. Numerous crepitant and bubbling rales could be heard over both lungs. Over the right upper lobe posteriorly bronchial breathing and increased whispered voice with egophony were present. The apical cardiac impulse was not felt, but the left border of dullness was 12 cm. from the midline. The trachea was in the midline. The heart sounds were of good quality. A loud rough systolic murmur was audible in the fourth interspace at the midsternal line where a friction rub was also noted. Blood pressure was 115/50 in both arms. The abdomen was distended and tense with marked edema of the abdominal wall. Liver and spleen were not felt, and there was no evidence of shifting dullness or fluid wave. There was marked edema of both legs, including the thighs and of the penis and scrotum.

Laboratory Data—The urine had a specific gravity of 1.028 to 1.032 and all specimens contained 3 to 4 plus albumin. The urine sediment contained occasional granular casts, 0 to 5 white blood cells and 0 to 3 red cells. One plus bile was detected in one specimen. The blood findings were: red blood cells 4.5 million, hemoglobin 98 per cent; white blood cells 9100. The blood smear showed a differential count of 67 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes and 8 per cent monocytes. The stools were negative. Blood nonprotein nitrogen was 35 mg. per 100 cc. and total protein 4.94 gm. per 100 cc., with albumin 1.47 gm. and globulin 3.47 gm. per 100 cc. respectively. Blood Kahn reaction was negative. An examination of the sputum was negative for tubercle bacilli. Right

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thoracentesis yielded 125 cc of blood-tinged fluid which contained 0.48 gm ϵ^1 protein per 100 cc. Smears of the fluid sediment and guinea pig inoculation were negative for tuberculosis. Chest x-ray showed an area of homogeneous density involving the right upper lobe with displacement of the trachea to the right. The right lung, the left apex and left lower lung showed several areas of mottled linear density. The right costophrenic angle was obscured by thickened pleura and small amount of fluid. The left diaphragm was very irregular. An electrocardiogram showed right axis deviation, deep S_1 and S_2 , normal rhythm and upright T waves.

Course—The patient was given a high protein, low salt diet with fluids restricted to 1600 cc. On the third hospital day he suddenly complained of marked respiratory distress, and perspired profusely. The rectal temperature was then 102° F. The chest x-ray at this time showed a collapsed right middle lobe. The patient went into collapse and developed increasing dyspnea and fever. He expired the following morning.

DISCUSSION

The salient features in the history and physical examination are (1) aching and swelling of both ankles of sixteen months' duration progressively involving the legs, thighs, abdomen, scrotum, hands and face, (2) weight loss of 5 pounds, (3) a very recent respiratory tract infection, (4) obvious malnourishment, (5) cyanosis, dyspnea and distention of the neck veins, (6) asymmetry of the chest with evidence of consolidation or cavitation and/or atelectasis in the right lung, (7) a friction rub and systolic murmur in the precordial region.

Since the evidence points to a disturbance in the physiologic mechanisms relating to the formation of pitting edema, the differential diagnosis should include a consideration of the causes of anasarca. Compatible with this phenomenon are

- 1 Congestive heart failure of many etiologies, e g, valvular disease, myocardial disease, constrictive pericarditis and so forth
- 2 Cirrhosis of the liver
- 3 Renal disease including glomerulonephritis, pyelonephritis, polycystic disease, Kimmelstiehl-Wilson's disease, renal vein thrombosis, and other causes of the nephrotic syndrome such as heavy metal intoxication and amyloidosis
- 4 Nutritional disorders (wet beri-beri and nutritional hypoproteinemia)

The laboratory data provides information of considerable value. The urine shows a good concentrating power, despite marked albuminuria and casts. One specimen contained bile. The blood is normal except for a slight monocytosis. The absence of nitrogen retention is noteworthy. There is a marked decrease in total blood protein with a reversal of the albumin-globulin ratio. The chest fluid has the characteristics of a transudate with a low concentration of protein. It is pertinent to ask whether the fluid obtained by paracentesis was bloody throughout or whether the blood was consequent to the technic of paracentesis.

Answer. The fluid, as first obtained, was bloody; it became clearer after movement of the needle

The negative examination of the sputum for tuberculosis is not necessarily significant since only one sputum was examined. Furthermore, the cough was nonproductive. Study of the gastric contents for tubercle bacilli would have been of more significance.

Of great value are the x rays which show a homogeneous density involving the right upper lobe, with displacement of the trachea to the right and areas of mottled and linear density in the right lower lung field. There is also evidence of fluid in the right pleural space, and mottled density in the region of the left apex and in the left lower lung. The findings thus indicate a process involving the lung bilaterally, with atelectasis of the right upper lobe. Focusing attention, for the time being, on the pulmonary process, we must consider the following conditions in its differential diagnosis:

1. Tuberculosis
2. Bronchiectasis
3. Primary carcinoma or metastatic malignancy particularly of the miliary variety
4. An acute pulmonary process of bacterial, viral or fungous origin.
5. Pulmonary processes secondary to disease elsewhere such as congestive failure or pulmonary emboli
6. Extraparenchymal thoracic tumors, such as neurofibromas, dermoid cysts and the like.
7. Silicosis and rarer pulmonary disorders such as beryllium poisoning and bronchiolitis obliterans should also be mentioned

The combination of extensive bilateral pulmonary disease and generalized edema with low total blood protein, reversal of the albumin globulin ratio and albuminuria help rule out many of the conditions listed above, such as carcinoma and other tumors, acute pulmonary infections, pulmonary emboli and primary pulmonary disease with the exception of tuberculosis and bronchiectasis, although one must always bear in mind that two or more diseases may coexist and yet be totally unrelated from a pathologic point of view.

One may exclude heart disease in general as the cause of these phenomena, since the present illness up to the time of admission is singularly devoid of dyspnea, orthopnea, cardiac pain, history of hypertension or other manifestations of heart disease. The only positive cardiac findings were the left border of dullness at 12 cm and a murmur and a friction rub in the fourth interspace. These signs and dyspnea, or orthopnea and cyanosis are explicable on the basis of the patent pulmonary pathology. The electrocardiogram which probably reflects a positional distortion of the heart, perhaps related to the pulmonary process, is of no particular diagnostic value except to help exclude conditions which show low voltage, such as constrictive pericarditis,

myxedema and extensive myocardial disease. The normal quality of the heart sounds, furthermore, justifies this interpretation.

Liver disease, such as cirrhosis, may also be excluded. The spleen is not enlarged, there is no evidence of portal hypertension, the blood is normal. Generalized edema and marked albuminuria are not usually found in hepatic cirrhosis. It should be remembered, however, that pulmonary or peritoneal tuberculosis occurs not infrequently in patients with cirrhosis of the liver.

There are several features which militate against nutritional disorders as being the underlying basis for this clinical picture. The history provides no evidence of an inadequate diet. Furthermore, on physical examination there is no other evidence pointing toward a vitamin or protein insufficiency. This is important since malnutrition results in multiple deficiencies.

We must now consider the kidneys as a source of the edema. It is obvious that, with continued loss of protein through the kidney, one might reduce the blood protein concentration to a point sufficient to account for generalized anasarca. This occurs classically in the nephrotic syndrome of chronic glomerulonephritis, amyloid nephritis, lipoid nephrosis, Kimmelstiehl-Wilson's syndrome. Unless we are prepared to make two diagnoses, the pulmonary lesion renders most of these possibilities unlikely except for amyloid nephrosis.

It is probable that the pulmonary process is of long duration in view of the fact that the right chest shows collapse of the upper rib cage. The long clinical course, the physical findings, and the picture of the lungs by x-ray are consistent with the diagnosis of chronic pulmonary tuberculosis with cavitation of the right upper lobe. The negative sputum and the absence of cough, fever, chill and night sweats are not necessarily incompatible with such a diagnosis. As mentioned before, study of the gastric contents for tubercle bacilli might have yielded significant information. The weight loss is also consistent with a diagnosis of chronic fibroid phthisis. The clinical finding of a wheeze suggests bronchostenosis which might also be in accord with atelectasis and fibrosis of the right upper lobe.

If we accept tuberculosis as the probable nature of the pulmonary disease we can readily relate the renal pathology and anasarca to it by making a diagnosis of *amyloidosis*. The latter is a well known complication of low-grade chronic infection. The terminal picture is of no particular interest except that the evidence of collapse of the right middle lobe associated with shock, dyspnea and rising body temperature points to a terminal pulmonary process.

Clinical Diagnosis

1. Nephrotic Stage of Chronic Glomerulonephritis
2. Fibroid Phthisis

- 3 Exudative Pulmonary Tuberculosis
- 4 Bronchiectasis
- 5 Pulmonary Atelectasis

Discusser's Diagnosis

1. Pulmonary Tuberculosis, bilateral, with cavitation of the right upper lobe, and bronchostenosis
2. Renal Amyloidosis

Pathology

- 1 Diffuse healed and active pulmonary tuberculosis with cavitation.
2. Tuberculous bronchostenosis of right upper lobe with atelectasis
- 3 Generalized amyloidosis with amyloid nephrosis
- 4 Focal necrosis of liver and slight acute intrahepatic pericholangitis

COMMENT

This case was presented in order to stress the importance of considering the complication of amyloid deposition in any chronic disease. Amyloidosis presents the following important clinical features. Eighty per cent of the instances of amyloid disease of the kidney, spleen and liver occur in association with pulmonary tuberculosis. Other conditions with which amyloidosis may be associated are pulmonary infections such as abscess and bronchiectasis, chronic bone infections such as osteomyelitis, malignant lesions, such as leukemia, Hodgkin's disease and multiple myeloma, subacute bacterial endocarditis, and other chronic systemic diseases such as syphilis, malaria and gout. More rarely amyloidosis occurs without any definite underlying disease.

In most patients, the presence of amyloid deposits is only of pathologic interest and causes no overt physiological disturbance, however, in some patients the clinical picture is characterized by edema formation, albuminuria, and at times by kidney failure. The deposition of amyloid is often sufficiently widespread to involve the kidney, liver, spleen and more rarely other organs. The chemical nature of the deposit has not been fully elucidated, but it has been established that the substance or substances in it are combinations of protein with sulfate bearing polysaccharides which are related to chondroitin, sulfuric acid and heparin. The deposition of this material occurs when there are alterations of antibody-antigen combination since it takes place almost always in conditions in which the immune mechanisms have been subjected to prolonged stimulation as in chronic infection. As many as 20 per cent of all cases of chronic tuberculous infection are said to show amyloid deposits of some degree at autopsy. It should be borne

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in mind, however, that amyloid deposits will often clear rapidly following eradication of the underlying infection or other processes which lead to their deposition

Important in the diagnosis of amyloidosis is the Congo red test. The technic and results of this test have recently been studied ^{1, 2}

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MISCELLANEOUS

OBESITY AS A MANIFESTATION OF NEUROSIS

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In publications on obesity comparatively little attention has been given to its psychological aspects, exceptions being Bruch,^{5 6 7} and Rennie¹⁰, yet obesity is related to eating, and eating and subsistence are among the most basic of human needs. In the life history of the individual the ingestion of food is one of the earliest adaptations to the environment, following only the establishment of respiration and the control of temperature. Throughout life the acquisition, reception and ingestion of food are strongly tinged with emotion.

For the purpose of this discussion the obese person is one who is fat and who comes to the physician for reduction in weight. In common with the rest of the profession, I cannot speak of obesity in general, as one speaks of rheumatic heart disease, since many and perhaps the large majority of obese persons do not consult a doctor about their weight. Two types of adiposity have been distinguished, the exogenous and endogenous types. The latter is a heterogeneous group characterized by various anomalies of the metabolic and endocrine systems. The exogenous type is prevalent and the endogenous form is relatively rare.

These terms are confusing and mean little. Actually the distinction is between obesity with lesions or abnormalities of function and obesity without clear evidence of these. The accepted terminology is objectionable because it implies that fat can be manufactured internally out of nothing. Instead of the term exogenous obesity I prefer the phrase *obesity of the common type*. Since most of my obese patients have been women I am excluding men from this discussion although my experience confirms the observation that psychogenic influences can be demonstrated in the obese of both sexes (Bruch⁷, Rennie¹⁰).

The large volume of scientific work which has been done on the total and intermediary metabolism of fat in normal and obese people has been reviewed elsewhere (Du Bois⁹, Rony¹¹, Conn⁸, Newburgh¹²). Some of it, however, needs to be evaluated in relation to the principle of the conservation of energy. This and other aspects of obesity have not been adequately discussed in relation to psychogenic factors. The following discussion is designed to fill this gap.

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PHYSICAL ASPECTS OF OBESITY

Obesity and the Conservation of Energy—The principle of the conservation of energy is simply that energy cannot be added to or subtracted from a closed system except through the external environment. A teakettle full of water is such a system. The only way to add calories to the water is to supply them from the environment, for instance, by setting the kettle on the stove. Once the water is hot, the only way to cool it is to take the kettle off the stove and permit the calories to radiate into the cooler atmosphere of the room. If the water is put into a thermos bottle, which prevents radiation in or out, it will stay at the same temperature indefinitely, that is, it will neither gain energy nor lose it. The human body is a closed system, which can store calories in the form of foodstuffs as well as in the form of heat. The energy of food can be added to the system only by means of the ingestion of food calories, and energy can be removed only by dissipating calories into the environment or by the performance of mechanical work. The only practical way to increase the loss is to increase the physical exertion. Therefore, if fat is to be removed from the body, fewer calories must be put in than are taken out, or more calories must be taken out than are put in.

From our knowledge of the basal metabolism it was first thought probable that the obese person might become fat because of a reduction in the output of calories as shown in the basal metabolism but, in spite of a large volume of investigation, this assumption has never been verified. The same is true of the specific dynamic action of foodstuffs (Rony¹⁰). Hypoglycemia is accompanied by obesity in the rare case of an organic lesion of the pancreas but acts by increasing the intake of food. It increases the appetite, or drives the patient to eat as a method of preventing the attacks.

Thus the basal metabolism of obese persons does not differ on the average from the normal, but this fact does not mean that the output of calories per hour is the same as in similar individuals of normal nutrition. The basal metabolism is expressed in terms of body surface and thus is increased in obesity because of the accumulation of inert tissue in the form of fat. The basal metabolism is, therefore, greater than would be expected from the mass of functioning tissue which utilizes oxygen. Assuming that the twenty-four hour metabolism is proportional to the basal metabolism in obesity, the output of calories is greater than it was before the accumulation of the excess fat.

This fact may be illustrated in the case of patient A. C., who reiterated that she did not eat enough to maintain her weight. This may have been true at the time of treatment, but could hardly be accepted for the past, in view of her 341 pounds. This woman was 5 feet 10 inches in height, and she weighed 180 pounds before she became fat. Assuming that her basal metabolism was normal according to the usual standards we can multiply this by her body surface of 2 square

meters and find that she eliminated at rest 74 calories per hour. After she had gained weight to 340 pounds she had a surface of 2.62 square meters and eliminated 97 calories per hour. Thus her expenditure of energy under standard conditions of rest, had increased 31 per cent. Therefore, she could have maintained a positive energy balance by two means only either by eating more or by exerting herself less, than when her weight was normal.

Actually she did both. When she was becoming fat she customarily drank two quarts of milk a day while lying in bed. Besides food she took two or three alcoholic drinks a day plus a weekly indulgence in a larger amount. She also reduced her output of calories drastically. By long professional habit she was a night-owl and, when she gave up her work, she continued to stay awake most of the night, reading a novel in bed. The result was that she slept the entire morning and part of the afternoon. On several occasions she overslept a 5 p. m. appointment. She also had a habit of lying in a warm bath, smoking and reading for an indefinite period. Thus she could readily retain her weight in spite of a 31 per cent increase in her basal metabolism.

Since no defect has been found in the basal metabolism of fat people, attention has been directed to their muscular efficiency. Evidence has been reported that obese persons perform work with less expenditure of energy than normal individuals. This finding has not been substantiated by later observations. It is probable, however, though hard to prove, that the obese person has a greater mechanical efficiency in another sense. She not only refrains from muscular effort as much as possible but also economizes in the use of it when she exerts herself. As in the old adage, she uses her head to save her hands. Either form of increased efficiency, if proved, would merely give rise to another question. Why is the food intake not adjusted to the decreased output of energy, so as to maintain a normal amount of adipose tissue? In other words, what interferes with the usual process of homeostasis, by which the appetite adjusts itself to the bodily needs?

In addition to the above, the intermediary metabolism has been intensively studied. One theory holds that there is some positive attraction by which fat is deposited and retained in the tissues more readily than in the normal individual. The fat deposits can be viewed as more or less independent of the energy exchanged after the manner of a lipoma, to cite an extreme case. Such a tumor satisfies its demands for fat, irrespective of the energy requirements of the rest of the body. The other extreme is the one which appears probable from existing evidences that the fat deposits are at least as sensitive to the overall requirements for energy in the obese as they are in the normal individual. An intermediate position might be tenable in which the fat deposits exert a special attraction in the obese, but are still responsive, though less so than normal, to the energy requirements of the body. The rare cases of lipophilia in which excessive fat is laid down in one part of the body and not in another might suggest this possibility. A similar conclusion might follow from an example cited by Rony¹⁰ of

a woman who had a piece of abdominal skin transplanted to her hand. Later when she accumulated abdominal fat, this piece of tissue became obese, but not the rest of the hand. It is well known, further, that sexual differentiation includes differences in the distribution and amount of adipose tissue. Unfortunately for the understanding of obesity, this lipophilic action has not been demonstrated in the ordinary case. Obese persons of all types, according to Newburgh,¹³ lose weight at a rate which can be predicted from the difference between their intake and output of energy. That this loss is at the expense of fat and not of other tissues is borne out by the fact that the obese individual remains in nitrogen balance in the face of a sharp reduction of caloric intake. This reduction is greater than the normal person could tolerate without destruction of body tissues.

Another possibility is that obese persons have an abnormally high concentration of foodstuffs in the circulating blood or tissue fluids, a concentration which exceeds the capacity of the organisms to use the foodstuffs for current needs, or to deposit them as glycogen. Such a mechanism is suggested by the work of Long and his associates (Brobeck⁴) who trained rats to eat the twenty-four hour allowance of food in a short period. The trained animals had a greater rise in the respiratory quotient after the ingestion of glucose than did those which were not trained. This observation indicates an increased capacity to convert carbohydrate into fat. Many fat patients behave somewhat like the trained rats, in that they eat a light breakfast, very little lunch, and then make up for it at dinner. Thus, they go through all the motions of reducing without losing any fat. Aub¹ has advocated a low calorie diet divided into several meals a day as a treatment for obesity.

At this point we must not forget the conservation of energy. Suppose the patient maintains a constant weight with three equal meals a day, and then continues to eat the same amount every twenty-four hours, but consumes most of this in one meal. The fat which is laid down after the heavy meal must inevitably be oxidized during the rest of the twenty-four hours unless she reduces her output of calories by an amount equal to the fat deposited. In other words, she must exert herself less in order to retain the fat.

With respect to other disturbances of the intermediary metabolism it is sufficient here to quote the statement from Rony's discussion¹⁰ that "there is no uncontested evidence of any specific disturbance in the intermediary metabolism of fat that could be regarded as a *major cause* of obesity."

Obesity and Endocrine Disturbances—We may now discuss the part which is played by the internal secretions in the development of obesity of the usual type. Here we have to guard against another fallacy: endocrine patients are obese, therefore, obese patients are endocrine. This reasoning becomes still less tenable when we reflect that

only a small proportion of patients with manifest endocrine disturbances also have obesity. Many endocrine diseases provide examples of lean patients as well as fat patients. Most diabetics are thin, but some are fat. Destructive lesions in the neighborhood of the pituitary gland can produce either Fröhlich's syndrome or Simmonds' cachexia. Both variations have been reproduced experimentally in animals. In a series of hypogonadal dwarfs I recall some who are fat, some who are emaciated, and some who have the normal amount of fat. The same variation occurs in women after castration or the menopause. The only endocrine disturbances which are conspicuously associated with obesity are Cushing's disease, destructive lesions of the hypothalamus and emaciation. Many women with thyroid insufficiency are fat, but scarcely fat enough to be called obese. Patients with myxedema need not be obese. In general, the endocrine disturbances affect the distribution of fat more than the total accumulation.

The fact that many endocrine disturbances can be associated either with obesity or the reverse might be explained on the theory that a hormone can act on obesity in one of two opposite directions. It is more probable however, that the action of hormones is complicated by other influences, notably psychogenic factors. These can be demonstrated as an important part of the etiology of many diseases of internal secretion, most readily in Graves' disease or disturbances of gonadal function.

Obesity which is demonstrably of endocrine etiology is rare even in an endocrine clinic, whereas fat people constitute a large section of the general population. In ordinary obesity very little evidence of endocrine disturbance can be found. The obese woman has normal skeletal and sexual characteristics. She tends to remain single but in many instances has married and borne children. Usually she has her menarche at the expected time and, as in two of my patients, her menstrual cycle may remain completely undisturbed even when her weight exceeds 300 pounds. When menstrual irregularities occur, they appear to be secondary to the obesity, because the menstrual cycle can often be restored simply by getting rid of the fat (Labbe¹⁰). Such a secondary effect of obesity induced by overfeeding upon the estrous cycle of guinea pigs has been observed by Papanicolaou.¹⁴

A hormone which controls the accumulation of fat would have to do so as explained, through its physiological effect. It is not enough to say that a person is fat, and has an endocrine deficiency; this deficiency must be shown to be related to the obesity either through a direct effect on the various processes concerned in the metabolism of fat or through an indirect effect on the appetite or on the total exchange of energy. Such an effect has been demonstrated in hypothalamic syndromes, but cannot justifiably be extended to other types of obesity without further evidence. Even in the special cases mentioned the hor-

monal control of the adiposity has not been shown. If and when such a hormone is isolated and prepared for clinical use we have a right to expect that it will act like insulin or estrogens, that is, it will produce the desired effect in proportion to dosage. Too little of this hormone should get rid of some fat, but not enough, too much should get rid of too much fat, and the proper dosage should bring about a normal weight.

The fact that such a hormone has neither been isolated nor demonstrated is no proof, of course, that it does not exist. The practical point is that the physician is expected to act as if he had an effective preparation in hand ready to administer to the obese patient. Such an expectation is often implied, not only by the obese woman but also by the doctor who refers her for treatment. To meet this requirement the physician has only a limited number of potent endocrine preparations at his disposal.

Of these the most promising is desiccated thyroid. This reduces weight but mainly in those patients in whom the insufficiency is marked enough to be detected clinically. Depression of the basal metabolism is no evidence in itself of thyroid insufficiency, unless it is well below minus 20 per cent (Boothby³). If the low basal metabolism is not due to thyroid insufficiency, it is not influenced by thyroid medication as a rule, and the extract has no effect on the body fat. Patients who have clinical myxedema can be restored to normal in respect to their clinical condition and basal metabolism by means of 2 or 3 grains of desiccated thyroid a day. The usual obese person shows no such effect. I recall a fat dietitian who took 8 grains a day (measured in dry weight) and its effect was no greater than so much milk-sugar. A patient came to the wards of the New York Hospital some years ago, she had taken 30 grains of desiccated thyroid a day for years, at the end of which she still weighed over 300 pounds. An obese patient now under my care stated that she required 30 grains daily of Armour's thyroid in order to lose weight. Some patients with Graves' disease are fat. Estrogens are equally ineffective, even when given in large enough amounts to produce their characteristic biological effect, as shown by the vaginal smears. Gonadotropins and pituitary preparations, whatever effect they may have in women, do not of themselves influence the body weight.

It often happens, of course, that an obese patient receives an endocrine preparation of some sort and loses weight. But this is no evidence that the preparation has any biological action on the fat apart from its psychotherapeutic effects. When the emotions are involved, as they usually are in any deviation from health, it is enough that the patient should believe in the remedy to produce a psychological effect on the disease. If endocrine preparations were not available for the treatment of obesity the patient would probably be equally benefited by some other form of medication.

In short, it is still a question whether the vital processes which are involved in obesity of the ordinary type are normal, or whether they are characteristic of the obese. So far as present evidence is concerned, it is unnecessary to postulate an abnormality (Newburgh¹⁸) According to von Noorden as cited by Du Bois,⁹ the ingestion of 200 calories a day in excess of the energy requirements is enough to lay down 17 pounds of fat in twelve months

Hypothalamus—Lesions of the hypothalamus such as tumors, in sections or injuries, are known to be followed in the human by pronounced obesity. Similar effects produced experimentally in the rat by Smith²¹ were shown by him to be independent of the hypophysis, and this conclusion has been confirmed by recent work, as summarized by Long and his co-workers.⁴ These authors ascribe the obesity to the ravenous appetite of the experimental animals, and conclude that it is due to a disturbance which primarily involves the quantitative control of the food intake. Others have suggested that the hypothalamic lesion is associated with a defect in the ability to oxidize fat or in the mobilization of fat reserves. Action on the glands of internal secretion other than the hypophysis has not been excluded.

Disturbances of appetite, sleeping and physical activity can be observed in human obesity of the ordinary type. How much they have to do with the hypothalamus is not known. This region contains the centers for the coordination of emotional activity, and its known functions provide a means of coordinating psychic determinants with their physical expression in the form of obesity.

Familial Aspects of Obesity—It is well known that obesity runs in families, although apparent exceptions to this statement are often observed. This fact does not, however, exclude additional mechanisms for the development of obesity, at most it describes how a predisposition can be transmitted from one generation to the next. In using the heading "familial" I wish to emphasize that transmission can take place in one of two ways or both of them at once, by genetic inheritance, or extra-genetically through the medium of the family life and its social and cultural setting (Richardson¹⁸). Evidence for both forms of transmission are available for obesity (Rony¹⁰ Bruch⁶).

Genetic inheritance of obesity has been studied in a special strain of yellow mice. In human beings the comparative weight of identical twins also suggests a hereditary factor in the Mendelian sense. Such twins tend to retain a similar body weight, in the absence of severe illness, to a much greater extent than nonidentical twins or siblings. It is not clear to me, however, whether these statistical results are due to genes or to some other factor. Identical twins are essentially a duplication of the same individual, they regard themselves as one, and are so treated by other people. Thus the emotional environment to which they are exposed is the same. Favoritism on the part of a parent, for

instance, is scarcely possible because of the lack of distinguishing characteristics and because sibling rivalry due to difference in age or sex is eliminated. Instances of identical twins who were separated at an early age and yet continued to have the same weight far into adult life have been reported to show that the environment has little effect compared to the hereditary factor. Such observations to be conclusive should include twins who have been separated at birth, because the mother-child relationship in earliest infancy (Bruch⁶, Rubble¹⁷, Waller²³) is of great importance for the neuroses of adult life.

Studies have also been made of the family incidence of obesity with the result that a correlation has been observed between the build of the parents and that of their offspring. Transmission is said to follow a Mendelian pattern through the medium of one to four genes.

It is possible to assemble equally strong evidence in favor of transmission through extragenetic channels. Bruch⁶ has made extensive studies of the "family frame" of obese children including statistics which show an increased incidence of obesity among the parents. These families gave abundant indication of transmission from mother to child through the special emotional relationship which exists between them.

Transmission of obesity through the family environment can be pictured in the case of the adopted child of foster parents. When a blood relationship exists, as in the usual case, it facilitates the transmission through psychological channels because it intensifies the emotional relationship between the generations. Thus the two points of view are compatible. The modern definition of an inherited constitution puts psychological traits on a par with physical characteristics. The manner in which the inheritance is expressed in the offspring is unknown, whether through the endocrine system, the various metabolic processes or through the nervous system. Among the activities of the nervous system must be included those which mediate the formation of a neurosis.

OBESITY AS A MANIFESTATION OF A NEUROSIS

Obesity of the *common or exogenous type* may often be regarded as the physical expression of a neurosis, this seems to me to be true of the majority of obese patients whom I have had the opportunity to observe. The reason both for the accumulation of fat, and for the difficulty in getting rid of it, can often be described in psychological terms as shown by Bruch for obese children.^{5, 6, 7} Rennie¹⁸ describes obesity in adults as an emotional disturbance. In evaluating the evidence it should be borne in mind, as stated below, that a neurosis can exist either independent of, or coexistent with, abnormalities in the physiological mechanisms.

One characteristic of neurosis in general is that the patient usually suffers. The suffering is not like the pain or discomfort of organic disease, but it is of a peculiar intensity and highly distressing. Another

characteristic of a neurosis is its destructive quality, the patient suppresses a part of her personality in order to function better with the remainder. This is a pathological adjustment and can be maintained only because it offers a psychological gain to the patient, who chooses subconsciously the lesser of two evils. This gain can be accomplished through symbolism as will be described below.

Neurotic characteristics are extremely common in obese women as shown in the following examples.

Patient A. C. says that the fat *affects her pride* and she has to laugh it off. She has been bewildered for seven years, threatening to engulf herself with fat. She did not weigh herself for two years, it was too much like reminding herself of a cancer. She has been large for a long time but she is becoming gargantuan and is feeling the situation, whereas formerly she laughed it off. The fat, she says, has been destroying her. Actually it was destructive in more ways than one, it forced her to abandon her professional career, which was one of her two great passions in life, and it was accompanied by incipient hypertensive cardiovascular disease and breathlessness at night in which anxiety could not be distinguished from cardiac attacks.

A large proportion of obese women have *symptoms of anxiety*, for instance, patient S. P. She has a rapid pulse in the morning and finds herself holding her breath in order to control it. She gives a classical description of a premature beat. She feels "jittery and trembly" inside and can find no resting place, if she sits down she wants to move. Additionally, she has been wondering if her family knew that she was receiving psychiatric treatment. Something stuck in her throat like a lump of cotton and she could not swallow. She felt that way as a child when she had done something which she did not want her parents to know about.

A *sense of guilt and depression* is common, the same patient stays away from the doctor when she has broken diet and is gaining weight. She has lost only a pound and a half in four weeks, feels guilty and depressed and weeps silently. "Who am I for the doctor to bother with so much?" She always had an "inferiority complex." She keeps saying, "It is all my fault."

This patient's self-depreciation is clear in other ways. She went to see a man to consult him about an historical paper which she was writing and she felt "about as high" to his presence; yet she found that she knew more about the subject than he did. She has read about the superego and feels the description fits her exactly. The center of gravity is outside of herself. It is what is expected of her and as a result she has no life of her own. She is like the automaton in her dream who raised her head as if pulled by strings—could that be herself? She admires her secretary who acts as she likes and does what she wants to do, who saw her man went out after him and got him.

Like many other obese women she feels depressed. This began a few years ago when she found that she could not do what really interested her. She found

herself in the wrong mold, she was a school teacher but wanted a home, cooking and children to care for. Her chief trouble is that she has little ahead, no sense of direction in her life and little desire to push forward. "Always there used to be something beyond, now there just isn't any more."

Eating acts for her like an *anesthetic*. She kept herself so busy with her work that she did not have time to think of anything else. She was never trim, she said, and she was conscious of the fact that men do not like fat women. I then remarked that no one compelled her to eat and she explained that, "when you're hungry you can think about things which you do not want to admit, one sort of anesthetizes oneself by eating." She eats because she is unhappy or dissatisfied or has nothing to do. After she has had a difficult committee meeting and is angry she is likely to eat sweet things like lemon pie or sago pudding.

Her eating has a compulsive quality. After a visit to the doctor she did not feel the need to eat for a few days, then she began to have extreme restlessness, almost an obsession. She threw everything to the winds and ate as she pleased. Similar ideas are expressed by other patients. Mrs. Albert M. says that when her people are working she can reduce but when they are not doing so she feels that she has to eat. "I get such a funny spell then if I don't eat right—it's my imagination. If I don't eat right I get excited, I get upset, I imagine I am going to die, I have lots of worries, I can't put that worry out of my mind. Maybe there's going to be a war—money—I get all upset and I have to take the milk." Another patient, Miss H. B., is a young woman having an ardent affair with a man who refuses to marry until his mother dies. She says, "If I am nervous or worried about anything I have a terrible desire for food, especially sweets. I just have an idea that I want to gobble."

Reverting to patient S. P., she has the feeling when she eats, "Well, I'll never get this again, there won't be any of it left tomorrow." If they offer her a second helping of pie she thinks that she had better take it for the same reason, or else because the next piece won't be so good. She eats sometimes as if that were the last piece of food on earth. Recently she thought that in losing the emotion which enveloped her father she was losing the satisfaction of eating. She does not mean that she stuffs herself but she has a tremendous craving. It is such an emptiness, as if everything had been drained from her and only the husk left. Even as she thinks about it she could weep. It must be just as bad, she says, as a man who is addicted to drink.

The idea of *food as an addiction* is expressed by many obese women. L. S. says "When a person has a drug or alcoholic habit something can be done about it but when you're addicted to food they haven't learned to control that. I've just realized that I have a large appetite. I think that I eat because I am bored. I can diet for three months and lose 30 pounds but then I start eating again. There ought to be some medicine for this. It is just as bad as a drug addict."

Obesity serves as a *protection* and one indication of this is the fear of reducing weight which is expressed by some patients.

Patient A. C. had a "funny" feeling between sleeping and waking, an intense fear and depression. She might be getting thinner and thinner until she vanished. She is shrinking to nothing and cannot stop it, it is the fear of death. She also has a fear that after a while she will begin to tolerate the reducing diet and get fatter again. When a famous actor dies after an operation she attributes his death to the fact that he had reduced 100 pounds in weight.

The same idea is expressed by Mrs. A. W. Formerly eating was one of her greatest pleasures. She refuses to be hungry again. "If you're not hungry," she says, "you can go through with other things." If hungry she might go on a diet, lose weight, then on two-thirds of a diet, then nothing at all. She would starve to death. She will not reduce and run the risk of getting sick again.

Obviously fat is a *protection against men and marriage*, many obese women use it in this way. Usually they are intrinsically good looking, as can be demonstrated by early photographs, and in the absence of excessive fat they have no difficulty in attracting men if they wish to do so. The husband in one instance feels critical about his wife because she is fat and fears that this means that he is disloyal to her. She says to him that if he really loves her he will do so regardless of the fat. Here she is using her fat as a test of her husband's love. Other patients say that they are not really fat or do not "think fat," implying or stating in so many words that people should like them in spite of the obesity.

Patient S. P., quoted above, felt and knew that she was not attractive because she was fat. She was so conscious of her size that she would not allow herself to be interested in men. Her ideals were impossible: three-fifths of a loaf, she says, were not enough, actually she got nothing. Her weight has always hindered her in the things which she wanted to do; she always wanted a child of her own. When her father bathed her as a child she wanted him to admire her body. This idea is tangled up with the process of reducing. On being asked if she meant that her father would admire her body if she reduced she said "No, he would love me just the same."

Eating as a *substitute gratification* is very clear in her case. Many things which she did such as school work and eating were from frustration, they helped her to take care of other drives.

She was always eating or doing something when she was frustrated. The fat is in her way; she has to exert herself so much she had to get large clothes which do not fit. Obesity, she says, is a disease. She has a craving for affection which nothing seems to satisfy. What she gets does not satisfy her. She lost weight at a time when she felt very grateful for some practical medical advice and information. She then felt tenderness and affection and thought that if she had an object for this she would never care whether she ate or not. She is not interested in eating when she has someone to care about; for instance, when she was helping the boy who stuttered, she forgot to eat her lunch. Her loss of weight was possible only because something kept drawing her back to the doctor's office. As long as she felt that the doctor cared it made a difference to her. When she felt that he lost interest she stopped losing weight or began to gain again. It is the old story of reaching out for affection. Her secretary who was interested in her reduction of weight had the same effect. She says that her loss of weight was not scientific because it was done to please the physician. She should be able to lose it whether anyone cared or not. She did lose 53 pounds and nothing can take that from the record, at least from the physician's record. All her life she has been striving to satisfy herself by overdoing things because of the lacks she felt in herself. The eating was part of that although it started when she was small. Eating is a sub-

stitute for sexual satisfactions, there are so many things in the interviews to show this. One would hardly expect it to begin at such an early age. The same is true of affection. She had affection from her father. She concedes that she has in effect denied the existence of her face and says that back of that has been all this fat.

Obese women in two cases had *phantasies of pregnancy* associated with eating and abdominal fat.

Patient A. C. dreams that she is as light as a thistle-down. She sees her neck and shoulders which are getting thin. She is pleased but she knows that there is a bulge below in the region of the abdomen. She is anxious and fearful that her body could not get any thinner than that.

Patient S. P. has a complicated dream about spies in which the spies turn out to represent the fetus and the fetus is equated with a lump in the intestine. In another dream she stops at a fruit-juice stand to get scraps for her dog, but there are none. Also she wants to get rid of her suitcase which she is carrying around. Then she sees herself standing against the white tiles, the middle part of herself in profile, very thin and slender except for a bulge of fat around the middle. She says to herself, 'I will have to get rid of that.'

With both of these dreams the fat has disappeared from the body except in the region which would be occupied by a pregnant uterus. In the second dream the wish to get rid of the suitcase has more than a suggestion of parturition, which appeared very clearly in previous dreams.

Later patient S. P. was able to describe her conscious reaction to being fat. Pregnancy was out of the question because she had passed the menopause. She has thought about my suggestion that her fat is tangled up with the idea of pregnancy and she thinks that this is true. When she eats as she should not, whatever fat she puts on is around the middle and right away she thinks to herself, regardless of what her intellect tells her, "Well, I wonder, do you suppose that I am pregnant?" She was careful of her diet and did lose 2 pounds, then she neglected to eat roughage and became constipated. She felt all bloated up, counted the months and thought that it was time for pregnancy to happen. At a lecture she felt faint, went into the ladies' room and vomited and then worried all the more about pregnancy. Even now she is all puffed up in the middle. She has this feeling every time she adds a little weight.

Examples could be multiplied to show neurotic symptoms in the obese, the destructive effects of the obesity, anxiety, guilt, self-depreciation, depression and a compulsive type of eating analogous to alcoholism or a drug addiction. That the neurosis affords a psychological gain is indicated partly by the fear of losing weight. Fat is used as a barrier against men and marriage and against other affectionate relationships of adult life. Two patients revealed phantasies of pregnancy, associated with eating and abdominal fat.

One reason for overeating is the association in the popular mind between fat and strength, typified by the word "stout." This is now a euphemism for fat, whereas formerly it meant strong. This mental association can be observed with almost any mother of a fat child when the latter begins to lose weight. Two of the patients cited above equated a reducing diet with death and suicide.

Eating to the obese woman is not a matter of appetite alone, if appetite is defined as a zest for food. The dishes which she prefers are one indication of this, these are essentially the same as those which are chosen by the obese child (Bruch⁶), such as candies, sweets, pies, cakes, soft drinks and milk. This is not the sort of food which appeals to an adult palate. Moreover, eating to the obese is not a matter of hunger, because this term implies a physiological need. Hunger is stilled when the need is met, but the desire of the obese woman for food is never satisfied. She eats as if to fill a boundless void. It is true that most obese women like the taste of food, but some of those who "gobble" are indifferent to the taste.

Enjoyment of food is not necessarily an indication of a physiological need, it is well known that the appetite can be destroyed by emotion and it is equally true that it can be enhanced by the same influences.

The strength of the craving for food and the equation, food equals affection, suggest a deprivation early in the life of the obese individual. This probably occurs at the time when the reception of food is indistinguishable from the reception of affection, that is, early in infancy. Deprivations in later childhood such as scarcity of food, the social and other handicaps due to poverty and withdrawal of affection, reinforce the earlier deprivations or provide a new starting point.

Two of the women cited above had phantasies in which they associated pregnancy with eating and abdominal fat. This may be an example of the use of a *subconscious symbolism to compensate for frustration*. The symbolism invokes a theory of pregnancy which is widespread in the mythology of primitive peoples, and is prevalent among very young children of our own culture (Waller²³, Rose²⁰). A like symbolism in patients who have anorexia nervosa has been observed by these authors and also by Masserman.¹² This disease has many characteristics which suggest that it is the negative equivalent of obesity.

In the neurosis which accompanies obesity the underlying dynamics can be demonstrated only by detailed case reports. Such a report in the case of S. P. is in preparation for publication elsewhere.

The neurotic personality of the obese woman as indicated in the above examples is not rare or exceptional. In my experience the same pattern can be demonstrated, if only in a fragmentary manner, by most obese women who can be induced to talk at length about themselves. How universal or specific the pattern may be is a matter of opinion at the present time and experience in the future.

Obesity as a Psychosomatic Unit—According to the above evidence, obesity can be regarded as a component of a neurosis, the physical expression of which is the accumulation of fat. By the latter term I mean all the bodily processes which are concerned in the activity including the over all exchange of energy and the formation, storage, mobilization and oxidation of fat. The

the physical side is whether these processes are characteristic for the obese as compared to the person of normal nutrition. If not, the relationship between the neurosis and its physical expression is extremely simple, the patient eats more food than she utilizes. Even if the fat metabolism is pathological in the obese, this is no evidence against a psychosomatic relationship, it means only that the relationship is more complicated. Analogies for this statement can be found in diseases which have known psychogenic components, such as allergy, peptic ulcer or hypertension. Additional evidence is needed in obesity on both sides of the question. Psychological data should be easy to obtain because the material is abundant and relatively accessible. As in many other diseases the distinction between so-called organic changes and the psychogenic factors should be replaced by a unified concept in which all types of evidence are given their proportionate weight.

Treatment—The first requisite for treatment is to understand the etiology of the disease, and in so far as this is psychological the treatment should be psychological also. From the physical point of view the therapeutic problem in the common type of obesity can be stated very readily, it is to induce the patient to ingest fewer calories than she eliminates. Solution of this problem is the reverse of simple because attempts at reduction in weight encounter psychological resistance. If the patient could reduce merely because the doctor tells her to do so she would not get fat in the first place. Or she does reduce by virtue of the doctor-patient relationship but relapses after an initial loss of weight. Furthermore, the question arises as to what sort of treatment the patient needs the most. She presents her problem as that of excessive weight but may indicate later, as did the patient S. P., that the fat is a relatively minor consideration in comparison with other effects of the neurosis.

For medication various endocrine preparations may be used and in my experience one is as good as another. They should be given with an eye to the psychological effect and not from any great expectation of a biological action on the fat deposits. Vitamins are needed for protection against a deficiency when the diet is reduced. They help also to reassure the patient against the supposed damaging effects of the diet. As an additional reassurance it is well to inform her that vitamins are necessary for the oxidation of foodstuffs. Benzedrine is widely used and seems helpful in preventing excess sleep and in increasing physical activity. I am not impressed with its effect in reducing the appetite.

Medical and dietary treatment is a form of psychotherapy in addition to its specific effects. Every measure which is taken to reduce the weight should be considered from this point of view. Reduction of weight is accomplished through the doctor-patient relationship which may be highly complex, as illustrated in the statements of the patient S. P. above. Among the difficulties is the profound sense of guilt often

felt by the patient when she eats in excess of the diet. This sensation does not prevent her from overeating and may even have the opposite effect. If more extensive psychotherapy is to be used I suspect that it may be an advantage to leave the dietary control entirely in the hands of the patient.

The technic of psychotherapy through the medical and dietary treatment is based on well defined general principles which have been stated by Levine¹¹ and Binger,¹² but in practice this treatment must be highly individualized according to the physician, the patient, and the relationship between the two. Treatment should also be related to the social and economic disabilities of the obese person and to her past or present relationship both to her family of childhood and her family of marriage (Richardson¹³). When the obesity or the accompanying neurosis present a severe handicap in living, prolonged psychiatric treatment should be considered, especially for younger people. Obesity is one of the conditions which should stimulate still further the current interest of psychiatrists and internists in methods by which psychiatric insights and technics can be adapted to the everyday practice of medicine.

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For many decades now, it has been believed that various types of diseases, infections, traumas or debilitation might induce the neurocirculatory asthenia syndrome. Actually, these things rarely were found⁷ *in themselves* to initiate the asthenic state. While a long-standing infection for example might aggravate mild or latent neurocirculatory asthenia, it never was found to produce the disease *de novo* unless, and only unless, the patient reacted *emotionally* to his disease, or, to put it more crudely, the patient who develops such a state in the course of an infectious disease does not do so because of the direct effect of pathogen or its products on his nervous or cardiovascular system but because he has become afraid of his fate, the expectation of pain, or the like. This fact could have been determined long ago if investigators had carefully and minutely questioned a limited number of patients rather than attempted to assess hundreds of them from amassed charts.

It must be emphasized that any patient suffering from either acute or chronic neurocirculatory asthenia invariably suffers from a partial derangement of the functional relationship between cortical and hypothalamic activities.⁸ This relationship may be disturbed by a *diminution* in cortical function, which is usually the case, or conceivably by *intrinsic* derangement of the hypothalamus itself. Such derangement has been observed in each of the hundreds of patients with neurocirculatory asthenia whom the author has seen.

Finally, it must be understood that acute neurocirculatory asthenia is identical with the psychiatric entity known as "acute anxiety neurosis" whenever the latter has autonomic reference in the cardiovascular system. The relationship is as simple and as complex as that. However, it has not been the author's finding⁹ that *chronic* neurocirculatory asthenia was due to some external event involving the patient. Rather, it seems that the chronic disorder represents a hereditarily determined one in which the patient is rendered abnormally susceptible to the influence of external events which rarely would cause difficulty in the normal individual. There is, then, no permanent cure for all the visceral and somatic manifestations of chronic neurocirculatory asthenia.

The above remarks concerning the basic characteristics of neurocirculatory asthenia were included in order that it may be understood that, while the cardiovascular and respiratory symptoms of the patient with neurocirculatory asthenia are his most troublesome and focal complaints, their eradication would not leave the patient either well or happy. Furthermore, if surgical or chemical means could be found to obliterate only the cardiorespiratory manifestations of the disorder, it can be expected that new systems under autonomic control would then erupt. The cure of the patient with this affliction is dependent upon the institution of "cortico-hypothalamic balance" and not upon the alleviation of a peripheral focalized abnormality of an entirely deranged nervous system. With this limiting qualification always in view,

it becomes easy to understand the basic pathogenesis of the cardio-respiratory derangements

THE CARDIOVASCULAR DISORDERS OF NEUROCIRCULATORY ASTHENIA

As mentioned in the introduction, the cardiovascular difficulties occurring in neurocirculatory asthenia do not arise because of organic or fixed changes within the cardiovascular system. Thus it was found⁴ that the heart of patients may be not only negative to physical examination, but also to roentgenographic and electrocardiographic examination. If further proof were needed concerning the basic integrity of the heart and the blood vessels, the follow up studies of Grant⁵ furnish it. He found no greater incidence of organic heart disease in patients having neurocirculatory asthenia for at least seven years than in normal persons of the same age. Whishaw¹² studying 130 patients having the disorder for at least twenty years agreed with the findings of Grant. Therefore for an understanding of the precordial pain, cardiac arrhythmias, intermittent peripheral arteriolar constriction, hypertension and giddiness which may occur in the disorder it must be kept in mind that kinetic and not histological derangements must be sought.

Precordial Pain (Sharp, Transient Type)—In a recent study of a series of patients with neurocirculatory asthenia, it was found³ that approximately 88 per cent of them complained of intermittent precordial pain. Without much question, it is this particular complaint which brings the majority of patients with the syndrome to the interested attention of the internist.

In the past, little attempt was made to distinguish the two entirely different kinds of precordial pain from which the patient might have suffered. This omission of differential description undoubtedly led to the present day confusion concerning the nature of the precordial pain in neurocirculatory asthenia. Obviously, if two entirely dissimilar sensations were considered as identical, no simple pathogenic process could consistently explain both of them.

The most common form of precordial pain, experienced by approximately 58 per cent of all such patients,³ was sharp, piercing and transient, beginning in the nipple and penetrating deeply and directly into the chest. It is this pain which frequently makes the patient fearful of taking a deep breath or changing position. The author had the opportunity of examining many of these patients at the exact instant when they complained of the pain. Electrocardiograms were taken also at this time. Examination of the heart revealed either extraordinarily forceful cardiac contractions or electrocardiographic studies detected the presence of an arrhythmia (ventricular extrasystoles, a paroxysmal tachycardia and so forth) at the time the patients complained of precordial pain of this variety. Almost always it

served that when they complained of precordial pain they also exhibited cold, wet hands, accentuated tremor, profuse axillary and palmar perspiration and pupillary dilatation

The occurrence of some form of transient dysfunction and the appearance of the extracardiac manifestations listed above at the time these patients complained of precordial pain suggest two important probabilities, namely, that (1) the precordial pain was of cardiac origin and (2) that a neurogenic discharge mediated via the sympathetic system had occurred. It is my opinion that this episodic type of neurogenic discharge preceded and precipitated the temporary cardiac arrhythmia or abnormal contraction which then in turn led to the sharp type of precordial pain perceived by the patients. Furthermore, the occurrence of the entire train of events during bed rest or its equivalent indicates clearly that neurocirculatory asthenia is not exclusively a disease of effort.

Cardiac Arrhythmias.—About 22 per cent of all patients with neurocirculatory asthenia will suffer at times from transient arrhythmia. The most frequently observed variety was that of ventricular extrasystoles, next in frequency were paroxysmal auricular tachycardia, wandering auricular pacemaker and auricular flutter or fibrillation. I believe that any type of arrhythmia short of a ventricular fibrillation may occur in the neurocirculatory asthenic state.

The high incidence of arrhythmia in neurocirculatory asthenia herein reported does not coincide with some of the published reports^{13, 14}. This divergency may be due to the fact that my statistics were obtained from a series of patients who were observed constantly almost every hour of the day for a period of weeks. During this period, all patients were asked to report immediately any peculiar precordial sensations or perceived cardiac irregularities. When patients so reported, electrocardiographic studies were performed immediately. If the incidence of arrhythmia had been obtained only from the findings on initial physical and electrocardiographic examination or if the hospital pulse rate records had been employed exclusively to determine the presence of arrhythmias, it would have been almost nil. The diagnosis of neurocirculatory asthenia cannot be made too accurately from a single or even a series of brief cardiovascular examinations. The patient must be studied as a complete entity and the physician who concentrates on an abnormal cardiac sign to the exclusion of the personality and the general nervous system automatically fashions his own therapeutic failure.

Hypertension.—True hypertension as indicated by an elevation of the diastolic pressure above 90 mm. of mercury is an extremely rare finding in typical chronic hypertension. Occasionally, transient elevations of the systolic pressure above 150 mm. may be observed but invariably the diastolic pressure remains below 90 mm. When the systolic elevation is observed, almost always a tachycardia accompanies it.

Occasionally in acute neurocirculatory asthenia even the diastolic pressure may be elevated. I have seen several instances in which the diastolic pressure was over 110 mm of mercury. Here too, however, there is not only an accompanying tachycardia but also a profound derangement of the entire sympathetic system. With subsidence of the other symptoms and signs of the disorder, the blood pressure also falls to within normal limits.

Giddiness.—At least 70 per cent of patients with chronic neurocirculatory asthenia suffer at times from giddiness. This symptom is not vertigo but rather a sensation of unsteadiness or lightheadedness. Occasionally it became severe enough to make the patient feel that he may be fainting but rarely if at all does this occur. Ordinarily it is transient in duration, rarely lasting for over several seconds.

The occurrence of giddiness so frequently after change of position from the reclining to the erect state has led some investigators to postulate that it might be due to a form of orthostatic hypotension. MacLean and his associates^{11, 12} studied a series of these patients suffering from giddiness. They came to the conclusion that their patients became giddy primarily because of an abnormally reduced venous inflow to the heart from the inferior vena cava following assumption of the erect position. However, these investigators did not measure the venous pressure of their patients; hence their assumptions cannot be accepted until such measurements have been made. Furthermore, such patients differ quite markedly from persons with known orthostatic hypotension in several important respects. Thus the former patients never exhibited any localized or generalized deficiency in perspiration or hypotension and the giddiness experienced was always transient, occurring immediately after arising and disappearing in five to ten seconds. Moreover, giddiness was rarely the primary complaint, being only one of the typical manifestations of the syndrome.

Various experimental studies² were done on patients suffering from giddiness and rather interesting results were obtained. Although not all patients with neurocirculatory asthenia demonstrated hemodynamic changes preceding and accompanying their giddiness, a large enough number did to indicate that such changes frequently induced the symptom. These changes consisted fundamentally of a hyperactivity or over-response of the sympathetic nervous system to pressure or flow alterations occurring in the right auricle. The alterations themselves were normal and to be expected in all individuals but these particular patients reacted abnormally to such normal changes.

Thus it was found in many patients with severe giddiness that the change from supine to an erect position apparently did not cause any less flow to their hearts than in normal individuals. However the tense peripheral arteriolar constriction occurring in the giddy and following the apparently normal decrease in venous return

heart, was distinctly abnormal. As a matter of fact, arteriolar constriction was so severe that effective cerebral circulation was probably arrested. In short, the venous dynamics of the patient with neurocirculatory asthenia and the normal individual were identical following change of position. Their sympathetic responses to the venous change, however, were considerably different in that the sympathetic response of the normal individual was adjusted nicely to the venous change, and the response of the patient with neurocirculatory asthenia was exaggerated and symptom producing.

Intermittent Peripheral Arteriolar Constriction.—Almost all patients with neurocirculatory asthenia experience an occasionally intense coldness of the skin of the hands and feet. This rarely persists long enough or produces sufficient discomfort to embarrass them. Ordinarily it is a sign and not a symptom of the disease.

It seems quite certain for several reasons that this sign results from peripheral arteriolar constriction. First, the subcutaneous administration of atropine or scopolamine will effect a disappearance of the blanched and cold skin of the extremities. Secondly, if venous blood is obtained from the antebrachial vein of one of these patients who has cold hands, the blood will resemble arterial blood in its oxygen content—that is, it seems to have arrived in the vein by shunt rather than through the capillaries.

This form of peripheral arteriolar constriction is almost always accompanied by excessive perspiration. Furthermore, constriction usually occurs independently of exercise or effort but almost invariably after emotional tension. Frequently however it will occur in the absence of any perceived emotion either by the patient or the observer. It never occurs in the sleeping patient.

THE RESPIRATORY MANIFESTATIONS OF NEUROCIRCULATORY ASTHENIA

The patient with neurocirculatory asthenia may have two respiratory symptoms, namely dyspnea, either at rest or after effort, and a dull type of precordial pain.

Dyspnea.—The dyspnea of the patient with neurocirculatory asthenia is not caused by cardiac dysfunction. Experimental studies were made concerning this possibility and it was found¹ that no true cardiac disability was present in patients with neurocirculatory asthenia at the time they were suffering from dyspnea. Furthermore it was found² that the dyspnea could not be due to any defect in the lung or in the transport or exchange of the blood gases. What then is the cause of the dyspnea? From my own observations, it seemed apparent that the dyspnea of patients was due to psychogenic and neurogenic causes arising high in their central nervous system. More specifically, emotion, overt

or disguised, was the chief cause of the dyspnea during effort. When patients performed work which did not make them breathe more than the average person. But it must be remembered that their emotional responses might seem incomprehensible to the observing physician who may find it difficult to understand why the performance of a very simple exercise should evoke an emotional response. Unfortunately, however, the most innocuous effort can induce a tremendous emotional upheaval in the patient with neurocirculatory asthenia.

The writer recently introduced a simple procedure, the hyperventilation test for the objective evaluation of the respiratory status of the patient with neurocirculatory asthenia. It consisted of asking the patient to hold his breath as long as he could. The time was observed and recorded. After a period of three minutes the patient's pulse rate was observed and recorded. Then he was asked to breathe deeply for five times in forty five seconds. At the end of this time, he was asked to hold his breath again as long as he could and his pulse was again observed and recorded. Ordinarily a normal individual will gain 80 to 115 per cent in his breathholding ability after such hyperventilation although his pulse rate will not accelerate unduly. In those patients with neurocirculatory asthenia suffering from easily induced dyspnea however the breathholding after hyperventilation is not only increased less than 30 per cent but frequently is less than that before hyperventilation. Their pulse rate also usually accelerates markedly after the hyperventilation. A ratio designated as the hyperventilation ratio (H. I.) was obtained by dividing the breathholding time after hyperventilation (expressed in seconds) by the breathholding time observed before hyperventilation. Thus if a subject held his breath for a period of sixty seconds before hyperventilation and for ninety seconds after hyperventilation, his hyperventilation index was 90/60 or 1.5. As mentioned above, the normal individuals would have a hyperventilation index varying from 1.30 to 2.13 (i. e., 30 to 113 per cent increase) whereas severely dyspneic patients with neurocirculatory asthenia would usually have an index below 1.30 frequently below 1.0.

The hyperventilation test, because it gives a firm basis not only in the neurocirculatory asthenia state, can be used in cases in which both organic cardiorespiratory disease and neurocirculatory asthenia are present so that the latter disorder may be ascertained. That is, even such a patient also has severe neurocirculatory asthenia (many such patients do have) the use of the hyperventilation test enables the clinician to determine whether the dyspnea complained of is due to the organic or to the neurocirculatory. Dyspnea may appear in patients with neurocirculatory asthenia only during effort attended by emotion but it is not

tion occurring at bed rest. These attacks essentially make up the disorder known as the "hyperventilation syndrome." A considerable amount of work has been done on the etiology and pathogenesis of these abrupt attacks of tachypnea and dyspnea, which may continue long enough to produce tetany. However, the bulk of such studies has been on the carbon dioxide deficit in the blood of patients having a seizure. Without question, some of the symptoms of the hyperventilation syndrome are due to the resultant blowing off of carbon dioxide. But to believe that complete relief may be obtained by the administration of this gas is foolish if only because the tachypnea, dyspnea, tachycardia, excessive perspiration and tremor (so frequently seen in the hyperventilation syndrome) are not relieved by the gas. If they were, the therapist giving the gas would be hard put to explain why the respiratory symptoms not only initiated the syndrome but also led to the gas deficit. Certainly a process leading to a low carbon dioxide concentration in the blood could not be caused initially by a low concentration of the same gas. Actually, I found that attacks of hyperventilation are initiated by episodes of excess neurogenic activity which then lead to low concentrations of carbon dioxide in the blood. Furthermore, the entire process *seems* to subside because of the administration of carbon dioxide but actually the reassurance offered by the presence of the treating therapist plays a part. This may be proved in several ways. First, the administration of carbon dioxide to these patients rather rapidly decreases their tingling, giddiness and carpopedal spasm, but no commensurate changes occur in the dyspnea, tachypnea, tachycardia, excessive sudation or hand tremor. These latter manifestations disappear so very gradually that they seem less the result of the gas than of the presence of the physician. Secondly and more important, the administration of pure oxygen to the hyperventilating patient, while it does not cause the disappearance of the tingling, giddiness and carpopedal spasm as does the administration of carbon dioxide, does alleviate the total syndrome as quickly as the latter. The therapist would have discovered this simple fact long ago if he had considered the hyperventilating patient not only as a physiological phenomenon but also as a psychological one. It cannot be stressed often enough that the study of patients with neurocirculatory asthenia cannot be performed by a machine or chemical reaction alone—the thinking, observing, balancing eye of the human observer must also do its share. It is, for example, too much to expect an electrocardiograph to determine in each instance whether a tachycardia is of an emotional or organic etiology.

Precordial Pain (Dull, Prolonged Type).—At least 45 per cent of all patients with chronic neurocirculatory asthenia suffer at times from a dull, persistent, aching sort of pain of the left chest having its maximal intensity in the region of the left nipple. Its most frequent precursor is indulgence in vigorous exertion although the latter may have

occurred many hours prior to the onset of the pain. Characteristically, patients having this pain prefer to lie on their right side

Wood¹⁰ investigating the cause of precordial pain in patients with neurocirculatory asthenia observed in them frequently a type of respiration differing from the normal in that it was characterized by poor use of the diaphragm and very little excursion of the lower half of the thorax during the actual act of respiration. I have been able to confirm these important findings. Thus it was noted on inspection of patients having dull, precordial pain that they tended to breathe by lifting the upper third of their thorax. Many were found who were unable to breathe with the lower portion of the chest (so called diaphragmatic breathing). Fluoroscopic observations also indicated that these patients made little use of their diaphragm in ordinary or even forced breathing. Further evidence was obtained that they actually had poor control of their diaphragm as indicated by their inability to develop an expiratory pressure even half as high as that developed by the normal individual. Again, it was found that on maximal inspiration and expiration the patient having pain had a greater excursion of the upper third of his chest than of his lower third—a finding exactly opposite to that found in the normal individual. In other words, these patients had breathed with the upper third of the chest so long that they had developed a greater, hence abnormal, degree of excursion in this area.

The above facts while indicating without doubt that the patient having precordial pain (dull type) lifted the upper third of his chest abnormally in breathing did not prove that this intercostal method of breathing produced the dull type of pain. In experiments already reported⁴ I took a group of patients having pain and so immobilized their chests with adhesive or plaster that they were forced to employ the lower third of the chest in order to breathe. When this was done, almost all of the patients lost their pain within forty-eight hours. In another set of experiments, I immobilized a group of normal individuals in such a fashion that they were able to employ only the upper third of the chest in breathing. These normal individuals so treated were then made to indulge in rather strenuous exertion. Almost all of them were found to develop pain in the left chest after several days. The abolition and production of the pain simply by altering the type of chest breathing certainly suggested that the cause of the dull precordial pain was the patient's method of exclusive intercostal breathing.

Why this pain was almost always confined to the left chest could not be determined. It is probable, however, that there is excessive fatigue in the intercostal musculature of both sides in those patients habitually using only the upper third of the chest in respiration. The contraction of the heart on the left side, however, against the fatigued musculature probably raises the subclinical fatigue to the clinical threshold of pain perception. This possible mechanism might also serve as an ex-

planation of why patients having the pain insist on lying on their right side, thus removing the "trauma" of the heart beating against the left chest

THE TREATMENT OF THE CARDIOVASCULAR AND RESPIRATORY MANIFESTATIONS

Although different kinds of therapy have been used in the treatment of patients with neurocirculatory asthenia, they have been similar in one respect, namely, their usual failure in effecting good results. Certainly the exclusive use of drugs acting upon the peripheral ramifications of the autonomic system or drugs having a sedative effect are invariably followed by therapeutic failure. Again, the administration of any known hormone is also worthless. For a while, the employment of graduated exercises was thought to be beneficial but this was due to the fact that true neurocirculatory asthenia often was confused with the somatic and sometimes visceric weakness following prolonged infection, trauma or debilitation. The latter disorder is one that can and should be differentiated quite easily from neurocirculatory asthenia in view of the fact that it, unlike the latter, contains no elements of personality change and never exhibits the periodic neurogenic discharge so frequently found in neurocirculatory asthenia. Finally, few psychotherapists have published any convincing reports showing cures for patients with neurocirculatory asthenia.

It can be stated almost categorically that chronic neurocirculatory asthenia can never be cured in the true biological sense because, despite the *post hoc ergo hoc* assumptions of some psychiatrists, it appears to be a disorder which, in the main, is transmitted by heredity. Usually however, the patient with acute neurocirculatory asthenia, once the initiating agent is removed, completely recovers.

The aim of treatment, then, in chronic neurocirculatory asthenia is to give the patient not only an understanding of his disease but also the philosophy to bear it with stoicism. In order to accomplish this extraordinarily difficult task, the patient must first have complete and abiding confidence in his physician. However, it is not easy to gain and retain the confidence of these patients as is known by any physician who has attempted to treat them. Usually the patient's confidence may be gained if the physician (1) carefully questions and examines the patient, (2) *forecasts* the occurrence of manifestations which may take place, (3) promises no cure, and (4) carefully and simply explains the pathogenesis of the disorder to the patient. Forecasting of symptoms is important, for if and when they occur the patient then remembers that he was forewarned.

The physician who has treated only a few patients with neurocirculatory asthenia may be led to believe that, since they are afraid of having an organic disease, they will be improved simply by his telling

them their fears are groundless. Actually, the patient with the chronic form of this affliction does not want to hear a physician tell him that his disorder is functional. Accordingly, it cannot be too strongly stressed that the physician must "sell" the diagnosis of functional disorder to the patient, who subconsciously desires an organic disease or at least that some extrinsic factor be blamed for his illness. As a matter of fact, the reassurance phase of therapy resolves itself into a continuous and repetitious explanation to the patient of why he does not have organic disease.

In order to drive home the point that the disorder is functional, the physician also may have to precipitate or produce various manifestations of neurocirculatory asthenia in the patient in order that the latter may more keenly realize that the physician is correct. Thus benzedrine or caffeine may be given with the patient forewarned of its effects. Giddiness may be produced by the Flack procedure¹ and hyperventilation may be induced for demonstrative purposes.

Saccharine gentleness and utmost delicacy in respect to the sensibilities of the patient have been stressed by some therapists, particularly the psychiatrists. Undoubtedly, these patients like such therapeutic finesse and will love their doctor for it too. Actually, however, such gentleness and oversympathetic understanding defeats therapeutic progress. Successful treatment does not demand cruelty either but it does require a masculine type of firmness. The outside world is to be the milieu of these people and, although its crudity undoubtedly aggravated their constitutional defect, it avails them little to condone their physiological escape by treating them as precious children. It is the duty of the physician to inculcate some "steel" into these unfortunate people in order that they may endure their autonomic derangements with at least a modicum of human equanimity. When such patients are discovered having paroxysmal auricular tachycardia, syncope or a hyperventilation syndrome, the physician should be nonchalant, almost casual, in his immediate approach. Moreover, he should stress the essential benignity of these seeming physiological cataclysms not only after they cease, but also while they occur.

As this type of reassurance is carried on, every effort should be made to discover the presence of some external agent which might be inducing an attack. Remembering that the patient with chronic asthma may be upset by external events in the normal individual. This is the psychiatrist who, seemingly in the face of an external event, assumes a constitutionally normal prior emotional turmoil is detected as the external event responsible for its attack. If this cannot be done an at

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As this type of reassurance is carried on, every effort should be made to discover the presence of some external agent which might be inducing an emotional reaction, always remembering that the patient with chronic neurocirculatory asthenia can be upset by external events which might evoke no emotional upset in the normal individual. This last fact has been overlooked by some psychiatrists who, seemingly oblivious of the essential or basic triviality of an external event, assume that the patient had been hereditarily and constitutionally normal prior to the receipt of emotional upset. If an emotional turmoil is detected or discovered in the patient, the external event responsible for its genesis should be removed if possible. If this cannot be done an at

tempt should be made to talk the situation out with the patient in order that as tolerable a view of the situation as possible be obtained. But it must be remembered that, even if the emotional turmoil could be eradicated, the autonomic insignia of the disease will not be abolished.

The use of specific drugs to correct various cardiovascular abnormalities is not only limited, but unwise, unless the patient is told that they afford only symptomatic relief. Thus quinidine may be prescribed for paroxysmal auricular tachycardia if the latter is frequent and long lasting. An anticholinergic drug may be given for the peripheral arteriolar constriction and excess sudation. Sedation may be prescribed for sleeplessness. Otherwise the treatment is primarily that of inducing the patient (1) to accept the true nature of his disease, (2) to live with its symptomatology. Occasionally, an emotional turmoil also may be resolved by the physician. The after histories of patients with neurocirculatory asthenia as studied by Grant⁹ and Whishaw¹⁵ indicate clearly enough that there is no lasting cure.

The treatment of patients with the acute form of neurocirculatory asthenia, however, is usually successful, for they were primarily normal before they had received their damaging impact (usually of an emotional nature). Once the emotional turmoil is eradicated by the intrinsic forces of the patient or the external agent initiating the turmoil is removed, recovery is rapid and usually complete.

Treatment of acute neurocirculatory asthenia, then, consists in the detection and eradication or neutralization of the external agent which has deranged temporarily "cortico-hypothalamic balance." Supportive treatment by reassurance is very helpful for, as the intolerable situation inducing the abnormal state disappears or subsides, these patients are quite happy to learn that their disorder is a functional one. They are the patients who, as Rames and Kolb¹⁰ have found, will get well on verbal reassurance alone. Specific treatment for their cardiovascular complaints should be the same as that given to patients having the chronic form of the disorder.

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SYMPOSIUM ON TREATMENT OF COMMON CARDIOVASCULAR CONDITIONS

FOREWORD

DISEASES of the cardiovascular system continue to form one of the most important groups of cases seen by the general physician. The relative and actual increase in these diseases as the result of aging population trends seems certain to continue for many years. Numerous advances in the field of therapeutics during the war years suggest the presentation of a symposium on this subject.

Increasing optimism is the keynote in the management of patients with coronary disease and chronic (inactive) rheumatic heart disease. Recognition of the earlier manifestations of coronary disease and the milder cases of myocardial infarction has altered our prognosis in many of these cases. The importance of a detailed regimen for patients with the various manifestations of coronary disease, to fit their individual lives and to prevent the development of a cardiac neurosis, cannot be overemphasized. While no new therapeutic agent has been introduced for the treatment of acute rheumatic fever, prophylaxis in rheumatic fever and rheumatic heart disease has been proved of value in selected cases.

The careful correction of dental sepsis in patients with chronic rheumatic heart disease, using sulfonamide or penicillin therapy coincident with dental surgical procedures, offers the possibility of some reduction in the incidence of subacute bacterial endocarditis. The mortality rate of acute and subacute bacterial endocarditis has been materially affected for the first time by the introduction of penicillin therapy. With further improvements in technic and the availability of other antibiotics which will eliminate infectious agents not susceptible to penicillin, we can look forward to a favorable prognosis in many cases which are recognized in the early stages.

The introduction of glucoside preparations of cardioactive drugs has been a step forward in the t

failure The great variation in dosage, degree of absorbability and method of administration of such products, however, has produced confusion in the minds of many physicians The cardinal principles of digitalis therapy have not changed and old truths must be retold if we are to prevent difficulties in this field The importance of sodium restriction, fluid balance and dietary factors are becoming more generally recognized in the treatment of congestive heart failure Mercurial diuretics continue to play an effective role in this field More widespread knowledge and utilization of electrocardiography has resulted in better diagnosis and therapy in the cardiac arrhythmias Surgical therapy has proved effective in the cure and amelioration of symptoms in a small group of patients with congenital heart disease Discussion of these procedures is not within the province of this symposium

The increasing clinical recognition of pulmonary embolism in its various mild and severe forms has been an important advance in recent years, and inclusion of this subject is significant The apparent failure of early postoperative ambulation to decrease appreciably the incidence of pulmonary embolism is of interest A more fundamental approach to the problem of intravascular thrombosis seems essential if the incidence of this serious complication in both medical and surgical patients is to be lessened Knowledge in the field of peripheral vascular disease continues to grow and the early recognition of these diseases by the general physician is essential if a correct etiologic diagnosis is to be made and effective therapy instituted

No attempt has been made to cover all of the important cardiovascular conditions, and the large subjects of hypertension and cardiovascular syphilis have not been discussed It is the hope of the authors that the subjects chosen have been brought up to date and that practical suggestions in diagnosis and treatment have been presented

JOSEPH B VANDER VEER
Consulting Editor

THE TREATMENT OF BACTERIAL ENDOCARDITIS

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In the presence of a bacteremia, one of the more common sites for pathogenic organisms to localize and produce metastatic infection is the endocardium of the valve leaflets. Whether the endocarditis is termed acute or subacute depends on the nature of the infecting organisms. In *acute* bacterial endocarditis the pathogenic organisms are usually the gonococcus, meningococcus, beta hemolytic streptococcus, pneumococcus, Staphylococcus aureus or the influenza bacillus, although other of the more virulent pathogens may also infect the heart valves. The organisms causing *subacute* bacterial endocarditis are less virulent and the Streptococcus viridans and indifferent streptococci are the usual offenders. Occasionally, gram negative bacilli and gram-negative cocci of low virulence, as well as Staphylococcus albus, may attack the valve leaflets.

The purpose of this clinic is to consider certain fundamental problems of therapy and to discuss some of the more important factors involved in the successful handling of patients suffering from bacterial endocarditis.

SUBACUTE BACTERIAL ENDOCARDITIS

Subacute bacterial endocarditis, because of its greater frequency is more important than the acute type and will, therefore, be discussed first and in considerably more detail. In general, the problems of subacute bacterial endocarditis may be listed as (1) prophylaxis, (2) diagnosis, (3) treatment, (4) complications, and (5) follow up care.

PROPHYLAXIS

Chemotherapy in Rheumatic Fever—It is well established that rheumatic heart disease is, in the main, the result of repeated attacks of rheumatic fever. Since the majority of cases of subacute bacterial endocarditis occur in persons suffering from rheumatic heart disease

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obviously our greatest opportunity and responsibility for prevention of subacute bacterial endocarditis is in these individuals who have had attacks of rheumatic fever, or who have evidence of rheumatic valvular damage. That repeated attacks of rheumatic fever can be prevented by chemoprophylactic measures with the sulfonamides is now generally recognized,^{1 2} therefore, it seems advisable to employ this preventive measure in persons who have had previous attacks of rheumatic fever.

In general, it is best to administer sulfadiazine, 1 gm. in a single daily dose, throughout the entire year. It is true that the more severe streptococcal infections occur during the winter, but it is well recognized that the mild infections in the summer months are sufficient to reactivate a rheumatic process. Furthermore, it appears that the dangers of drug sensitivity are greatly increased by intermittent administration. This form of prophylaxis is not without certain untoward reactions³ from the drug and it is important during the first six weeks of sulfadiazine administration to make weekly studies referable to the white cell blood count, skin and temperature. If, during this initial period of time, there are no signs of drug intoxication, the chances of trouble in the future are negligible. In this connection, it is important to forewarn the patients as to possible toxic reactions to the drug, such as skin lesions, itching, and elevation in temperature.

Chemoprophylaxis in Certain Surgical Procedures—It is generally agreed that the upper respiratory passages and the mouth contain the most common portals of entry in subacute bacterial endocarditis. Since involvement of the endocardium by infecting pathogens is facilitated by previous valvular disease or by a congenital anomaly, it seems expedient that all such foci be removed as a prophylactic measure in persons with rheumatic valvular or congenital heart disease. The eradication of these foci is not without serious consequences as the non-hemolytic streptococcus is commonly present in these areas and operative trauma often results in a transient bacteremia. It has been found that bacteremia follows tooth extraction and tonsillectomy in approximately 70 and 30 per cent of cases respectively.^{4, 5} In a recent report⁶ of a large series of cases of subacute bacterial endocarditis, 20 per cent gave histories of tooth extractions or some form of dental manipulation within several weeks before the onset of the disease. These same authors⁶ pointed out that most edentulous patients who develop subacute bacterial endocarditis are infected with the enterococcus, rather than *Streptococcus viridans*, the latter being the most common causative agent of this disease in persons still having their teeth.

In view of the above, it appears advisable that all foci of infection, such as those found in teeth and tonsils, should be eradicated and every effort made to reduce the number of bacteria at the site of the proposed operation in order to prevent an implantation of the patho-

gens on the valve leaflets. The extraction of teeth, especially in the presence of infected gums,⁴ appears the most serious offender in this connection. Furthermore, the incidence of bacteremia seems to be greater when general anesthesia is employed and when more than one tooth is removed. Therefore, when advising the removal of teeth, it is well to request that local anesthesia be used and that not more than one tooth be extracted at one time. Obviously, every effort to clean up gingival infections should be carried out prior to surgical attack. In addition to the above, there is reason to believe that sulfonamides, given before and after such operative procedures, will decrease the incidence of transient bacteremia.⁷ Despite these precautionary measures, cases of subacute bacterial endocarditis continue to be reported⁸ following such procedures as the extraction of teeth. Nevertheless, sulfadiazine or sulfamerazine, 1 gm every four hours, or penicillin, 200,000 units per day in eight divided doses, for three days before and after extraction of teeth and removal of tonsils seems indicated in all patients with valvular or congenital heart disease.

Surgical Ligation of the Ductus Arteriosus—Numerous congenital defects have been found to permit the development of subacute bacterial endocarditis or endarteritis. Among these abnormalities patent ductus arteriosus is relatively rare but it is one in which surgery offers definite hope of cure. The effect of this arteriovenous communication upon the welfare of the patient varies largely upon the size of the ductus arteriosus. If the lumen of the ductus is great, there will be a large amount of aortic blood shunted into the pulmonary circulation thereby resulting in the development of pulmonary congestion and cardiac failure at an early age, resulting in subsequent death in approximately 80 per cent. Roughly one half of these patients succumb as a result of subacute bacterial endocarditis or endarteritis.⁹

Recent data have shown that the average surgical mortality in uninfected cases of patent ductus arteriosus is 8.5 per cent as compared with 50 per cent in the infected group.¹⁰ It would seem advisable in either event to resort to surgical intervention in such cases and preferably before the development of subacute endarteritis or endocarditis.

DIAGNOSIS

Theoretically the earlier the treatment is instituted the better the chances are for therapeutic success. The basis for this belief is the fact that the bacteria are soon covered by a fibrin platelet protectorate which thickens and thus prevents effective antibacterial therapy. Since, in many instances, it is difficult to establish a definite date of onset, it is our clinical impression that there exists little or no direct relationship between the duration of the disease and the outcome of therapy. Nevertheless, the chances of complications, such as mycotic aneurysm formation and congestive heart failure due to ulceration and perforation

of valves, are greater the longer the disease continues. In view of the problems associated with penicillin therapy, every effort should be made to substantiate the clinical diagnosis by cultural methods. Hence, the problem is one of (1) early diagnosis and (2) accurate diagnosis.

Early Diagnosis.—In order to establish an early diagnosis of subacute bacterial endocarditis, it is necessary for those of us in the practice of medicine to be familiar with its clinical manifestations and watch for the appearance of those symptoms and signs in persons who have the background for the development of the disease. It is not surprising that we encounter a variety of complaints and physical findings in this condition when one considers the fact that minute perivascular hemorrhages occur throughout the body of persons suffering from subacute bacterial endocarditis. In general, the clinical features of this disease may be divided roughly into three groups:

1 *Toxemia*—The chief symptoms resulting from toxemia are malaise, easy fatigue, weakness, loss of energy, fever, chilly sensations, joint or muscle pains, loss of appetite, nausea and loss of weight. On physical examination, one finds a pallor of the skin and visible mucous membranes and a loss of muscle tone. Petechiae often occur about the hands and feet and on conjunctival buccal membranes. Although these petechiae are usually regarded as toxic in origin, no definite proof has yet been presented.

2 *Embolic Phenomena*—Abdominal pain from infarction of the spleen or kidney and paralysis from cerebral embolism are among the common phenomena that result from emboli. Emboli to any artery may take place with symptoms in the area involved.

3 *Progressive Valvular Defects*—Shortness of breath, especially on exertion, is not only one of the first but also one of the most frequent symptoms of cardiac insufficiency connected with this disease. The associated murmur which reflects the valvular involvement is slower in becoming coarse in quality in subacute bacterial endocarditis than in acute endocarditis. This change is a valuable point and should be looked for in suspected cases of the disease.

Accurate Diagnosis—To definitely establish the diagnosis of subacute bacterial endocarditis, the clinical findings must be substantiated by at least two positive blood cultures. It has been estimated that the causative organism is isolated in the blood stream in over 90 per cent of such cases presenting conclusive clinical signs of the disease. Not infrequently, multiple cultures of the blood are necessary before a positive culture is obtained. We have found that the use of anaerobic cultural methods has given positive results in several instances when the aerobic cultures were negative.¹¹ The use of arterial blood has long been considered a method of choice in such cases where repeated venous blood cultures were negative. According to Beeson and his associates,¹² blood from the antecubital veins gives a colony count only

slightly lower than the arterial blood. These same workers showed that in bacterial endocarditis organisms are discharged into the blood from the endocardial vegetations at a comparatively even rate. Nevertheless, we have observed instances in which several blood cultures have been taken at different times in the same day with only a single culture being positive. This would suggest that the organisms may at times be discharged in showers, and repeated cultures in a single day are worthy of trial. It has been demonstrated that if diagnostic blood cultures are made at the beginning of the expected rise in temperature more positive results and higher bacterial counts will be obtained.¹⁸

The importance of making a bacteriological diagnosis in subacute bacterial endocarditis is more than one of academic importance, since two important factors in therapy are dependent upon the isolation and identification of the causative agent in each case of the disease, namely (1) determination of bacterial sensitivity to antibacterial agents and (2) discovery of induced drug resistance.

1. *Bacterial Sensitivity*—Obviously, the best results are obtained in cases in which the infecting organism is sensitive to the agent employed. Thus far it appears that only a small percentage of patients with subacute bacterial endocarditis are infected with penicillin-resistant strains of streptococci. In general, if the causative organism is inhibited by 0.05 units or less of penicillin per cubic centimeter of culture medium, one should expect therapeutic success with moderate amounts of penicillin. If more than 0.1 units per cubic centimeter is required for inhibition of the organism the chances of success are greatly reduced, even with the use of very large amounts of penicillin. From the standpoint of therapy therefore, it is important to know the relative sensitivity of the organism to penicillin so that dosage can be estimated. Furthermore, with the discovery of the variants of penicillin, such as penicillin X and streptomycin, it is possible to determine the sensitivity of the organism against several therapeutic agents and thus decide which drug to employ in a given case of the disease.

2. *Induced Penicillin Resistance*—At this writing, we have no indication as to the exact incidence of induced penicillin-resistant organisms in treated cases of subacute bacterial endocarditis, but we believe that resistance does develop in a small percentage of cases. This acquisition by the bacteria of increased resistance to penicillin is more likely to occur when relatively small doses of penicillin have been given over long periods of time. A safe rule to follow is that penicillin therapy be withheld if possible in all febrile patients with acquired or congenital cardiac lesions until a positive blood culture is obtained. Obviously, at times it is expedient that penicillin be started immediately and in such cases it is important that adequate doses of penicillin be employed.

TREATMENT

Choice of Drug—The successful treatment of a patient with subacute bacterial endocarditis is largely dependent upon certain factors inherent in the individual case. Therefore, in discussing the treatment of this disease it is well to emphasize the point that each case is to be handled as an individual problem, although certain basic principles involved in such therapy can be applied in general to all cases.

Penicillin—At the present time penicillin is the drug of choice in the treatment of subacute bacterial endocarditis due to the *Streptococcus viridans* or indifferent streptococci. Although extensive and conclusive statistical studies under uniform conditions are not yet available, it appears from a recent review¹⁴ of numerous preliminary reports that apparent clinical arrests have been obtained in approximately 56 per cent of the cases of subacute bacterial endocarditis. With properly conducted penicillin therapy, the percentage of clinical arrests will undoubtedly be raised to a much higher figure and more recent reports tend to support this view.

Penicillin Fractions—The question is still unanswered as to which of the better known penicillin fractions (F, G, K, and X) will prove most effective. Penicillin K seems relatively ineffectual while penicillin X appears to offer some additional hope.^{15, 16} The organism in one patient in our experience developed an increase in resistance to commercial mixed penicillin from 0.025 to 0.75 Oxford units per cubic centimeter after nine months of therapy. His sensitivity to penicillin X was tested at the end of this period and found to be 0.05 Oxford units per cubic centimeter. He finally responded to 600,000 units of penicillin X, given daily for twenty-five days. On death from cardiac decompensation four months later, he was found to have healed endocarditis. Another patient failed to respond to a similar course of therapy with penicillin X, in spite of a sensitivity of 0.05 Oxford units per cubic centimeter.

Streptomycin—Studies are now being conducted to determine the efficacy of streptomycin in the treatment of subacute bacterial endocarditis and preliminary reports are favorable. Since the toxicity of streptomycin is probably greater than that of penicillin,¹⁷ it is doubtful if streptomycin will replace penicillin in the therapy of subacute bacterial endocarditis for the average case, but should find use in patients whose organism is, or has become, resistant to penicillin and is sensitive to streptomycin. Many of the gram-negative bacilli and gram-negative cocci that occasionally cause this disease will possibly respond to streptomycin.

Heparin—Heparin, as yet, does not seem to be a proven adjuvant to therapy in this disease and is probably dangerous. The results of penicillin therapy alone^{6, 11, 14, 19, 20, 21} seem to be as good as the combined use of heparin and penicillin.¹⁸ In addition to the increased cost and

the difficulty in regulation of heparin there is a real danger of hemorrhage with its use. The increased capillary fragility combined with the emboli that occur in this disease and persist for as long as several weeks after therapy has been stopped, makes the use of heparin extremely hazardous. Hemorrhage about cerebral emboli is the most serious complication.

Penicillin Therapy—For the most part, the outstanding problems of penicillin therapy in this disease are (1) the daily dosage of penicillin, (2) the route of administration and (3) the length of treatment.

1. *Daily Dosage of Penicillin*—Theoretically, the daily dose of penicillin should be governed largely by the sensitivity of the organism to the drug. It should be remembered, however, that this test constitutes a biological measurement and is subject to certain inaccuracies inherent in this type of test. Furthermore, there is evidence suggesting that the different growth characteristics of organisms in broth and in the body account for the discrepancy between in vitro measurements and levels of penicillin required in the blood. Hence, we cannot be unduly influenced by the in vitro findings, but they may be employed as a rough guide to therapy. In general, it seems advisable to employ enough penicillin to obtain a blood level at least five to ten times the minimal amount effective in vitro.^{15 21}

This figure may have to be revised upward since adequate initial therapy should avoid the development of increasing resistance as well as the progression of valvular damage. Our present feeling is that at least 500,000 units per day should be given in cases with a sensitivity from 0.01 to 0.05 units of penicillin and this figure increased in proportion to the increased resistance. Doses as high as 10,000,000 units per day have been given successfully and without serious reaction.²²

2. *Route of Administration*—Several methods of administering penicillin have been employed successfully in the treatment of this disease. Theoretically it would appear desirable to administer the drug in a manner which gives rise to uniform and satisfactory serum levels, since it has been demonstrated that a continuous flow of penicillin is much more effective than equivalent amounts given intermittently.²³ Therefore the use of constant intravenous or intramuscular drips are recommended by many workers as the methods of choice. Nevertheless, penicillin, given intramuscularly every one to three hours, is being used with success by a number of investigators.

In addition, "booster doses" as recommended by Baehr²⁴ have been employed with apparent success. This method was devised of facilitating the sterilization of the lesion within the valve through greater penetration of the drug as the tonally high blood level several times a day. In a case of subacute bacterial endocarditis in which occurred following penicillin therapy, "booster

daily doses, at three hour intervals, of 62,500 units of penicillin were administered, together with two "booster doses" of 100,000 units each. In other words, 162,500 units were given every fourth injection.

There is some evidence suggesting that penicillin combined with beeswax and peanut oil can be given successfully at twelve-hour intervals.²⁵ At present, the oral administration of the drug does not seem practical in the handling of this disease, because of irregular absorption and the large amounts required for adequate blood levels. The oral route may eventually prove to be the method of choice.²⁶

CONTINUOUS INTRAVENOUS ROUTE—Early in our experience with penicillin in the treatment of this disease, the continuous intravenous route was employed routinely. Because of the technical difficulties associated with its use and of satisfactory results with the intermittent intramuscular route, we now seldom use it. It should be stated, however, that some workers still prefer to give penicillin by continuous intravenous drip, although it is acknowledged that from the technical standpoint this method is not the simplest. Its successful routine use requires skillful venoclysis technic and relatively close supervision of each case throughout the entire time of therapy.²⁷

CONTINUOUS INTRAMUSCULAR ROUTE—The continuous intramuscular route is being employed by a number of investigators. It is recommended that the daily dosage of penicillin be mixed in 250 to 500 cc of physiological salt solution and given through a number 19 needle, inserted into the muscles of the thigh. The site of infusion is generally changed from one thigh to the other every three to five days, depending largely on the amount of local reaction or discomfort. This method likewise requires special apparatus, and, in addition, constant attention day and night if the penicillin blood level is to be maintained uniformly high throughout therapy.

INTERMITTENT INTRAMUSCULAR ROUTE—Because of its ease of administration, the intermittent intramuscular route is the method of choice for the treatment of this disease with penicillin at the present time. Although it is agreed that this method gives satisfactory results, there is considerable variation of opinion as to the total number of injections in each twenty-four hours. Since there is little penicillin in the circulating blood one hour after injection and practically none at the end of two hours, it would seem advisable to administer penicillin at hourly intervals. Despite this fact, excellent results have been obtained by giving the drug intramuscularly every two or three hours. It appears impossible to recommend at this time whether one should employ eight, twelve or twenty-four injections intramuscularly per day in order to realize maximum therapeutic results. Certainly giving the drug every two hours should be a safe schedule on which to start therapy.

As indicated, penicillin, combined with beeswax and peanut oil, has been employed successfully in the treatment of this disease. By the

use of this preparation, it may be possible to limit the number of daily intramuscular injections to two. This method may eventually prove to be a most satisfactory way to treat cases with this disease.

3 *Length of Treatment*—Because there are no definite criteria for evaluating the status of the injection while penicillin is being administered, one of the most difficult problems in handling cases of this disease is deciding how long to continue the drug. From available data pertaining to this matter, it seems advisable, regardless of daily dose, to continue penicillin for at least fifty days.

Although many patients with subacute bacterial endocarditis respond to 200,000 to 300,000 units given for fourteen to twenty-one days, the general feeling is that the larger doses of 500,000 to 1,000,000 units should be given for a longer period of time. The danger from the progression of valvular damage with eventual death from decompensation and the development of resistance to penicillin by the organism, requires an adequate initial course of therapy. If relapse occurs after this first course of fifty days, the second course should be ten weeks with the dosage adjusted in terms of the organism's sensitivity. The physician should not be discouraged by several relapses since many patients have finally responded after four to six relapses from apparently adequate courses of therapy. Penicillin A and streptomycin, when available, may be of help in the therapy of relapses accompanied by a loss of sensitivity.

4. *Prolonging the Action of Penicillin*—As stated, it is necessary to employ repeated injections or continuous infusions of penicillin in order to maintain an adequate concentration in the circulating blood. This is a result of the cyclical rapidity of absorption, distribution and elimination of penicillin. It appears logical that a decrease in the rate of absorption of penicillin would permit the administration of larger doses at less frequent intervals. As already mentioned, this has been partially realized by suspending penicillin in a mixture of beeswax and peanut oil.

Since the elimination of penicillin occurs principally by renal excretion, it appeared natural that methods should be sought to reduce its rate of excretion. It has been found that if sodium para-aminohippurate is administered simultaneously with penicillin, it competes with penicillin for the same renal tubular excretory mechanism.²⁸ By so doing, the rate of renal elimination of penicillin is much reduced, thereby slowing considerably the rate of fall of blood concentration of penicillin. In this way the intravenous administration of sodium para-aminohippurate is capable of elevating several fold the blood concentration of penicillin over that which is obtained when penicillin is administered alone. The fact that this acid is relatively nontoxic in its use over extended periods of time. As yet the limited supply of material to us has prevented an extended clinical evaluation.

effectiveness in subacute bacterial endocarditis. However, there are several reports in the literature,^{21, 29, 30} suggesting its value in cases of this disease in which relatively high concentrations of penicillin in the circulating blood were desirable.

Eradication of Possible Foci of Infection.—Since certain focal infections may cause a reinfection of the heart valves, it is important that a careful search be made for possible foci of infection and their eradication effected if possible. This is best done while the patient is receiving penicillin. As indicated previously, the upper respiratory passages and the mouth, particularly the teeth, harbor foci which act as the most common portals of entry in this disease. Because of this, we have every patient thoroughly checked as to ears, paranasal sinuses, tonsils, gums and teeth. If there is any doubt as to whether a tooth is infected, we advise its extraction. This is well illustrated by the case of a 48 year old industrialist, suffering from subacute bacterial endocarditis, who had received two courses of penicillin with relapse. During the third course of penicillin therapy it was decided to remove several possibly infected teeth. Immediately after the extraction of an upper molar, a purulent discharge occurred from the maxillary sinus through the tooth socket which rapidly subsided. Treatment in this case was finished over one year ago and the patient is still free from the disease.

As pointed out above, subacute bacterial endocarditis may result from a pre-existing subacute bacterial arteritis. The two common arterial lesions in which *Streptococcus viridans* vegetations have been found are patent ductus arteriosus and arteriovenous aneurysm. Metastases of the infection to the endocardium occur and ligation of the ductus or removal of the aneurysm must be performed.

Combined Penicillin and Sulfonamide Therapy.—Because of the similarity of the therapeutic effect and the apparent complete compatibility of penicillin and the sulfonamides, their combined use in the more serious infections, such as subacute bacterial endocarditis seems reasonable. For the most part, evidence of their combination is based upon clinical experience and empirical reasoning, although experimental studies in vitro indicate a synergistic effect.³¹ Other workers maintain that the effect is purely additive. Although we have had but little experience with combined penicillin and sulfonamide therapy in cases of subacute bacterial endocarditis, we have seen several patients with acute endocarditis who did not respond to either drug alone but showed an immediate response to combined therapy.³² One of the main disadvantages of sulfonamide therapy in diseases such as this, which require relatively large doses over long periods of time, has been the danger of kidney damage. Whenever combined therapy is used, it seems best to employ a sulfonamide mixture containing equal parts of sulfadiazine and sulfamerazine.³³ By giving $7\frac{1}{2}$ grains of each drug

every four to six hours, it is possible to maintain an effective blood level of the combined sulfonamide with less danger of renal damage

Combined Fever and Drug Therapy—In 1937 Dry and Willius³⁴ concluded that fever therapy enhances defense processes in cases of subacute bacterial endocarditis. Two years later White³⁵ found that the antistreptococcal activity of sulfonamides *in vitro* were greatly increased by rises in temperature. Clinically, it was shown that although physically induced fever enhances the value of sulfonamide therapy in subacute bacterial endocarditis, the effect of combined fever-sulfonamide therapy has never appreciably reduced the mortality from this disease.^{36 37} More recently, combined fever and penicillin therapy has been suggested by results obtained against different strains of spirochetes³⁸ and *Staphylococcus aureus*.³⁹ Although we have not employed combined fever penicillin therapy in subacute bacterial endocarditis, such a combination would seem logical in certain resistant cases. Furthermore, if one considers the possible synergistic action between penicillin and the sulfonamides, the trial with combined fever penicillin sulfonamide therapy may prove more effective

COMPLICATIONS

Cardiac decompensation is the most common complication due to this disease. As noted above, this is related to the initial cardiac damage present at the onset of infection plus the damage resulting from the bacterial erosion and from the anemia. Even if bacterial resistance to the drug did not develop during therapy, the *early* and *adequate* treatment of the disease is necessary to prevent an increase in the amount of valvular damage. With the onset of symptoms of cardiac failure, all the common therapeutic measures should be instituted including low salt diet, digitalis, mercurial diuretics and aminophylline. It is possible to continue to give the patient a continuous drip of penicillin in 3000 cc. of fluid provided the salt intake is kept low and no salt is given intravenously.

Emboli become more common the longer the disease remains untreated or inadequately treated. Cerebral emboli and those to the bowel are the most serious in our experience. Recovery from the neurological symptoms of cerebral emboli is much more complete than from the symptoms of thrombosis due to arteriosclerotic arterial disease. Emboli to the eye usually cause permanent damage because of lack of collateral blood supply.

In one patient it was necessary to perform a femoral embolectomy on two occasions with eventual recovery of the patient. Her death finally occurred five months later due to cardiac decompensation.

Mycotic aneurysms are becoming much more common in our experience especially in those patients who have had the disease for a long period of time with frequent relapses. Treatment is

should be performed as soon as the diagnosis is made because their tendency to continually enlarge makes removal increasingly difficult.

Although continual fever due to penicillin was common when the commercial fractions were relatively impure, fever is rarely seen now due to penicillin alone. With the concentrated solutions needed for higher dosages, induration may occur at the site of the injection, especially if the injections are inadvertently given subcutaneously. These areas may cause a low grade fever and add confusion to the picture. The presence of low grade fever usually means a dosage of penicillin insufficient to control the infection. Streptomycin on the other hand is not infrequently accompanied by a rise in temperature.

Urticaria is seen as a reaction to penicillin and is seldom an indication for stopping the drug. Benadryl, 50 mg three times a day, may control the reaction, if not, the brand of penicillin should be changed. Only when an exfoliative dermatitis seems imminent, should the drug be stopped and later restarted when the reaction subsides.

Anemia is seen in those patients in whom the infection has been present for a long time. On a normal diet with supplementary vitamins and iron, the condition soon corrects itself without the aid of transfusion. If the hemoglobin is below 60 per cent, or fails to rise during therapy, the patient should be transfused, since chronic anemia is damaging to the myocardium.

FOLLOW-UP CARE

All patients should take their temperature at least twice daily for a period of three months after the cessation of therapy. If the patient remains afebrile for thirty days after stopping penicillin treatment, it is highly probable that the disease has been successfully arrested. The onset of a low grade fever in the absence of other causes is indicative of a probable relapse. The patient should be rehospitalized and daily blood cultures taken to confirm the suspected relapse before penicillin is started again. The importance of getting a positive culture cannot be overemphasized, since the dosage given in the next course of therapy depends on the sensitivity of the organism. The progression of the disease during the week or more that may be needed to obtain a positive blood culture is counterbalanced by the avoidance of an inadequate course of therapy. The development of fever is usually soon followed by bacteria in the blood stream, although we have seen in a single case seven months elapse with continued fever and negative blood cultures. Concerning relapses we have followed the general rule to start therapy within two weeks, even though repeated blood cultures may be negative.

Since one attack of subacute bacterial endocarditis does not seem to afford immunity against subsequent attacks, it is important to educate the patient as to the nature of his disease. He should be warned of

the dangers of trivial infections and of certain operative procedures, particularly those involving the mouth and throat. In this connection it is well to reemphasize that all bacterial infections, especially dental sepsis, should be treated adequately and if surgical procedures, such as extraction of teeth or removal of tonsils, are to be performed, penicillin should be given prophylactically as outlined above. Chemoprophylaxis with sulfonamides the year round seems indicated in most instances. Careful watch should be maintained for the signs and symptoms of cardiac decompensation, since its development is frequently hastened by the residual scar and fibrosis.

ACUTE BACTERIAL ENDOCARDITIS

Acute bacterial endocarditis is usually seen as a complication of one of the acute infectious diseases, such as pneumonia, meningitis or gonorrhea, but may occur during the course of a bacteremia in which the primary focus is often unknown, such as staphylococcemia. Acute bacterial endocarditis frequently occurs in a normal heart valve as opposed to subacute bacterial endocarditis which usually is superimposed on previously damaged valves. In view of the comparatively greater virulence of the organism in acute endocarditis, a more formidable course may be expected. Some of the cases are so rapidly fatal that they have earned the title of "malignant endocarditis." Prior to the advent of the sulfonamides, only an occasional patient was reported to have recovered from this disease. Many cases are doubtless undiagnosed at present, being successfully eradicated during the treatment of the primary disease. For this reason it is difficult to estimate the incidence and mortality of the disease.

Diagnosis.—Bacteremia is a prominent feature of the clinical picture of many of the acute infections, but it is only rarely that the endocardium is attacked. The absolute diagnosis of acute bacterial endocarditis must, therefore, rest on other criteria than positive blood cultures. Spiking fever with positive blood culture, plus a gradually coarsening murmur are found early. Later, embolic phenomena occur leading to the formation of abscesses containing the pathogenic organisms. Any patient having persistently positive blood cultures during apparently adequate therapy for pneumonia should be suspected of having acute endocarditis.

Treatment.—The treatment of acute bacterial endocarditis should consist of either penicillin or streptomycin, depending on the nature of the infecting organism. Thus far it appears that streptomycin is indicated in cases resulting from *Bacillus influenzae*, the *Brucella* group and possibly other gram negative organisms.

As stated previously, sulfonamides have been successfully combined with penicillin in cases of this disease that failed to respond to either

Adequate treatment of the primary process has undoubtedly reduced the incidence and mortality of acute endocarditis. In the presence of repeatedly positive blood cultures one cannot wait for the corroboratory evidence, such as coarsening heart murmurs and embolic phenomena, to make a diagnosis of endocarditis, but must treat the bacteremia alone. Specific therapy in the form of penicillin or streptomycin should be given or increased to amounts sufficient to control the fever and bacteremia. In the case of penicillin this is usually 500,000 units daily and for streptomycin approximately 3 gm per day. Such therapy should be continued for fourteen to twenty-one days, depending on the clinical response to treatment. Specific therapy should not be delayed until sensitivity studies are done, although it is important to make these determinations concomitantly to ascertain whether the organism is sensitive.

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PULMONARY EMBOLISM

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PULMONARY embolism is a frequent and often disastrous complication in patients with a variety of medical and surgical conditions. The importance of the problem raised by this complication is emphasized by the statistics collected by Barnes¹ which show that pulmonary embolism is the cause of death in more than 2 per cent of all autopsies. In one series (adults only) death was due to this cause in 6.5 per cent (Belt). Approximately 6 per cent of all postoperative deaths are due to pulmonary embolism, and the total incidence postoperatively (including both fatal and nonfatal cases) is 0.1 to 0.3 per cent in large surgical clinics.*

The magnitude of this problem has led in recent years to a large amount of study concerning the possibility of prevention or control of the factors giving rise to embolism. Much progress has been made, although the fundamentals involved in the thrombophilic tendency are but poorly understood. An attempt will be made in this discussion to survey the known etiological factors, the clinical features both of the preliminary thrombotic state and the embolism itself, and the treatment, prophylactic and otherwise.

ETIOLOGY

Thrombi which are potential emboli may arise in the heart or in any part of the venous system.

Cardiac Sources.—While emboli may arise in either side of the heart, only those from the right chambers, of course, can be responsible for pulmonary embolism. Nine cases out of 108 studied by Sagall, Bornstein and Wolff⁴ had such an origin. Mural thrombi in cases of cardiac disease are probably more common than has been appreciated. Garvin⁵ found that 34.4 per cent of 771 consecutive adult autopsied patients who died of heart disease had one or more such thrombi. They were found in two-thirds of the patients who had coronary artery disease *with* myocardial infarction and in one-third of those with coronary disease *without* myocardial infarction. One third of those with hypertensive and one-third of those with rheumatic heart disease also demonstrated mural thrombi. In syphilitic heart disease there was an incidence of one in five, but in chronic cor pulmonale and in subacute bacterial endocarditis they were an uncommon finding. In rheu

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matic heart disease thrombi occurred two and one-half times as often in patients with auricular fibrillation as in those with a normal cardiac mechanism. The probable significance of auricular fibrillation in the rheumatic group was also indicated by the fact that one or the other atrium was the site of the thrombus in 86.5 per cent.

The importance of coronary disease with myocardial infarction as a source for emboli is emphasized by the statistics of various authors^{5 6 7 8} which indicate that mural thrombosis is found in from 17 to 83 per cent of cases coming to autopsy with this condition. Nay and Barnes,⁹ in a study of 100 consecutive fatal cases, found that 37 per cent had thrombotic or embolic complications of all types, and pulmonary embolism occurred in fourteen. It is true, of course, that thrombi are found more often in the left ventricle and thus give rise to emboli in the greater circulation, but since the interventricular septum is frequently involved in myocardial infarction, right ventricular thrombi may occur, making pulmonary embolism from that source a possibility.

It is essential to emphasize that, while many of the pulmonary emboli in cardiac patients arise in the heart itself, a fair proportion come from the veins of the legs where diminished peripheral circulation is an important factor in their origin. This is true of patients with myocardial infarction as well as of those with other types of cardiac disease.

Systemic Vein Sources—Unquestionably the systemic veins, especially those of the lower portion of the body, are the commonest sources of thrombi which result in pulmonary embolism. This is illustrated by the study of 189 cases of fatal pulmonary embolism reported by Henderson.¹⁰ In his cases 227 sources of emboli were found, some of the cases having two or even three sites of thrombosis, and of these 196 (86 per cent) were in veins which are direct or indirect tributaries of the lower third of the inferior vena cava.

In Castleman's autopsy studies¹¹ the site of origin of peripheral venous thrombi is even further limited, since he found that the deep veins of the legs were the site in 95 per cent of the cases. This is in accord with the venographic studies of Bauer¹² which indicate that the *starting point* of the clotting process is in the lower part of the leg in more than 98 per cent of the cases. Appreciation of this fact is extremely important to the clinician as an aid to his vigilance in attempting to detect the earliest signs of the disease.

Mode of Origin of Peripheral Venous Thrombi.—Many questions remain to be solved concerning the origin of venous thrombi in the peripheral veins. In true thrombophlebitis it is easy to comprehend the likelihood of a locus for blood clotting. Processes that have their origin in this manner apparently result, however, in early fixation of the blood clot with less danger of embolic accidents. It is becoming

more and more evident that the particularly dangerous cases, and the most frequent, are those in which "bland phlebothrombosis" arises without evidence of early inflammation and in which the danger of a loose extension of the clot being swept into the blood stream is great. The clinical manifestations of the early stages of this process are extremely occult and constitute a challenge to the diagnostic skill of the physician

Factors in Increased Clotting Tendency—An attempt to understand the origin of bland phlebothrombosis has shifted the focus of investigation from inflammatory factors to a study of disturbances in blood clotting, since the latter is the more important causative mechanism. This increased clotting tendency has been referred to as the "thrombophilic diathesis." Progress along these lines of investigation has led to a realization that the factors involved are numerous and complex. A summary of the various potentialities now known to play roles of varying importance in the abnormal clotting process may be presented as follows

A. VENOUS STASIS

1. *Confinement to bed.* The diminished circulation in the veins of the legs on confinement to bed is undoubtedly a factor of great importance. It is lack of the normal "booster pump" action of the muscles that is most significant in this diminished circulation
2. *Posture in bed.* Elevation of the knees by pillows or other devices, as in the modern hospital bed, with pressure at the popliteal area, further favors stasis of blood in the calf muscles
3. *Diminished respiratory movement.* The effect upon venous return of the negative intrathoracic pressure resulting from normal inspiration is important, and this is reduced in the bedfast patient, especially with sedation and with restricting bandages which further embarrass respiratory movements
4. *Diminished muscle tonus.* This factor mentioned previously under bed rest, deserves separate consideration since it may be further diminished by sedation and by a lack of emphasis upon exercise and massage in the bedfast patient.
5. *Congestive heart failure.* Diminished circulatory rates in myocardial insufficiency may be largely responsible for the frequent venous thromboses of cardiac patients. Diminished muscle tone due to lack of exercise and prolonged bed rest are, of course, also factors
6. *Injury to venous endothelium.* Infectious, traumatic or chemical injury to the endothelium of veins may be responsible for blood stasis in some cases

B HEMATOLOGICAL FACTORS

- 1 *Increased platelet count* It has been demonstrated that there is a rise in the blood platelet count after childbirth and surgical operations. This rise begins about the fourth day, reaches a maximum on the tenth and returns to normal by approximately the twenty-first day. The time relationships involved correspond so well to the known incidence of postoperative and postpartum thrombo-embolic disease as to suggest an important relationship.
- 2 *Enhanced agglutinability of platelets* The agglutinability of the platelets increases under the same circumstances and with the same time relationships as does the increased platelet count.^{13 14}
- 3 *Hemoconcentration* This may be a factor of considerable importance, and is not infrequently an associated finding in patients with thrombo-embolic disease.
- 4 *Increased thrombokinasase* Injury to tissue would release this important element in the clotting process and disturb the balance which normally exists between it and heparin.
- 5 *Changes in the plasma proteins* An increase in fibrinogen and a shift in the albumin-globulin ratio in favor of globulin are known to occur postoperatively, and may be factors favoring thrombosis.
- 6 *Increased blood viscosity* An increase in blood viscosity, whether due to hemoconcentration, polycythemia or changes in the plasma proteins, may be of considerable importance. In polycythemia vera thrombotic complications are common.
- 7 *Digitalis administration* It has been demonstrated by several groups of investigators^{15 16 17} that digitalis has thromboplastic properties and antagonizes heparin. Whether this is a direct antagonist to heparin or acts through a neurogenic, vagal mechanism (deTakats) has not been settled.

C MISCELLANEOUS FACTORS

- 1 *Age* That age is a factor of great significance is demonstrated by the studies of Allen et al.³ Only 17.7 per cent of their patients with thrombo-embolic disease were under the age of forty. It may be stated also that *fatal* embolism is quite rare in the young.
- 2 *Weight* Obese patients are definitely more susceptible than are the nonobese.
- 3 *Malignant disease* Some statistics have indicated an increased tendency in patients with malignancy to develop thrombotic postoperative complications.³

The thrombus which arises in the peripheral veins, due to one or more of the factors listed above or to others at present unknown to

medical science, is frequently only loosely attached to the vessel wall. The basic clot or "white head" is composed essentially of platelets and leukocytes, and superimposed upon this there develops a collection of erythrocytes constituting the red, friable, "eel like" tail of the clot. The latter grows and waves in the current of the blood stream and may become 40 to 50 cm. in length. Under fortuitous circumstances it may become organized and eventually recanalized in the vessel of its origin, but it may, on the other hand, be swept from its attachment and carried in the blood stream to the right heart and pulmonary circulation to produce serious results.

The Pathological Physiology of Pulmonary Embolism—Mechanical blockage of the outflow tract of the right ventricle or pulmonary artery frequently results in immediate or nearly immediate death. In one series of 100 cases of pulmonary embolism² with a total mortality of 87 per cent, 8.5 per cent died in less than ten minutes and 33 per cent in less than one hour. Smaller emboli may result in only temporary circulatory embarrassment with recovery, or there may be evidence of obstruction of a portion of the circulation of one lung with pulmonary infarction. Infarction may be either hemorrhagic or anemic. Hemorrhagic infarction will occur only when there is secondary venous thrombosis.¹⁸

A number of factors are apparently involved when circulatory embarrassment results. These are not all comprehended under the single heading of vascular obstruction. Certain reflexes of an unfavorable nature would seem also to be involved and explain some of the discrepancies which have often been observed in attempting to relate the size of the embolus to the magnitude of its effects. Experimental evidence^{19, 20} tends to incriminate a reflex mediated over the vagus nerve producing bronchospasm and bronchial secretion. The afferent impulse may be dependent upon a rise in pressure in the right heart chambers. A pulmonocoronary reflex^{21, 22} may also exist and add vasoconstrictive myocardial ischemia to the mechanical difficulties under which the heart is laboring. The existence of this reflex has, however, been doubted by Katz,²³ since he finds that the electrocardiographic changes of experimental pulmonary embolism can be induced in vagotomized animals.

THE CLINICAL PICTURE IN THROMBO-EMBOLIC DISEASE

It is extremely important in considering the clinical features of thrombo-embolic disease to include a discussion both of the underlying thrombotic disease and of its embolic results. In fact, the former is far more important than the latter, since early recognition of the underlying process may lead to effective prophylaxis. Cardiac disease states as sources for emboli have already been referred to, and their clinical features are so well known as to require no emphasis here.

The features of phlebothrombosis in the peripheral veins, however, have not been stressed sufficiently in medical texts and are worthy of detailed discussion

Symptoms and Signs of Phlebothrombosis.—As has been stated previously, inflammatory features are most often lacking and the patient is therefore seldom aware of any discomfort due to the presence of this process in his leg veins. Nor is there any edema in the early stages, and careful measurements of the legs may demonstrate no increase in the circumference of the involved extremity. A low grade fever may or may not be present. Only when the thrombotic process has extended into the common femoral or pelvic veins do the features classically described under the term *phlegmasia alba dolens* become evident. The stages which precede this are the dangerous ones from the standpoint of potential embolism.

Careful study of the early stages of the thrombotic process in its commonest site of origin, the deep calf veins, has led to the recognition of certain signs which may aid detection before a calamitous accident has occurred. Homans' sign²⁴ has considerable value and consists in the eliciting of pain in the calf when the foot is forcefully dorsiflexed. Allen,²⁵ however, has found that only fifty-nine out of 202 patients showed Homans' sign in the early phases, but he considers it diagnostic when present. Moses²⁶ does not believe that this sign is specific even when present, and has described a series of maneuvers which he finds of great value in the detection of early disease. Three maneuvers are involved. The first of these consists in a careful search for tenderness in the deep posterior calf by direct compression with the fingertips in the *anteroposterior* direction. The second maneuver consists in firm compression of the calf between the fingers and the palm in a *lateral* direction. In early phlebothrombosis this is painless or relatively so, as compared with the first maneuver. The great majority of lesions which simulate incipient thrombosis are accompanied by considerable tenderness on lateral compression. The third maneuver in Moses' diagnostic study consists in a brief neurological examination (cutaneous sensation, position and vibration sense, and deep reflexes) to rule out peripheral neuritis, which may simulate thrombotic disease. The author has found this series of maneuvers of considerable value and believes it should receive widespread recognition.

Venography.—Diodrast injection of the major venous pathways from the ankle to the pelvis, with roentgen visualization, has been used to demonstrate the patency or occlusion of the veins and the extent of collateral circulation. The value of this procedure in the diagnosis of incipient thrombotic disease has been much disputed. Bauer¹² has enthusiastically supported it and has made a valuable contribution to our knowledge of the earliest stages of the process by its use. Some of the recent reports, however, have been discouraging, and the objections

have been summarized as follows ²⁶ (1) There is definite risk of either initiating or increasing the venous thrombosis (2) The examination is usually moderately expensive and requires material and apparatus not always available (3) False negative reports occur in as many as 33 per cent of cases and are especially frequent in the early stages of the disease (4) There is a large group of venograms in which the interpretation of the findings is extremely difficult. (5) Venospasm is frequently impossible to differentiate from organic occlusion (6) There are normally present at least six deep veins of the lower extremity, and all are seldom outlined at one time by the procedure. Hence it would appear that there is a limited field of usefulness for the venographic procedure.

Diagnostic Awareness—Probably most important of all in the recognition of phlebothrombosis is an awareness on the part of the physician of the potential occurrence of this disease, and a careful and repeated use of the signs mentioned in all cases which are candidates for its development in accordance with the etiological principles outlined. Even under these circumstances it must be admitted that there are, unfortunately many instances in which the process is so occult as to defy recognition until embolism has occurred. It is to be hoped that other means may become available in the near future for the early recognition of these unfortunate cases.

Symptoms and Signs of Pulmonary Embolism—The clinical features of pulmonary embolism are extremely varied. As already indicated, the large clots which produce complete obstruction of the main pulmonary artery cause immediate death. If the block is partial or involves one main branch, the syndrome described by White²⁷ as the "acute cor pulmonale" results. There is produced a combination of the manifestations of shock plus those of acute distention of the right side of the heart, often with signs of right heart failure. The features of forward and backward failure of the heart may be mixed in varying proportions. Precordial pain, dyspnea, cyanosis and other features closely simulating those present in myocardial infarction may cause considerable difficulty in differential diagnosis. Since myocardial infarction is not infrequent as a complication of the postoperative period in older individuals and since electrocardiographic changes may be present in both conditions the difficulties are considerably enhanced.

Embolism involving the lobar or smaller branches of the pulmonary artery on either side undoubtedly accounts for many so-called postoperative pneumonias. There is a sudden onset of pleural pain, dyspnea and cyanosis. Hemoptysis may or may not occur. Pleural friction sounds are often heard, and there are frequently found diminished voice and breath sounds and moist rales over the involved lung parenchyma. Roentgenological examination is often helpful, but daily examinations may be necessary inasmuch as infarcts are invisible or

ill defined during the first twenty-four hours²⁸ The lesion is always in contact with a pleural surface, the long diameter of the infarct being parallel to the largest pleural surface involved A pleural effusion may temporarily obscure the lesion Both oblique and lateral views may be necessary to reveal the characteristic sharp, convex outline of the medial margin of the infarct Incomplete infarcts disappear within a few days, and complete ones usually heal by linear scarring within

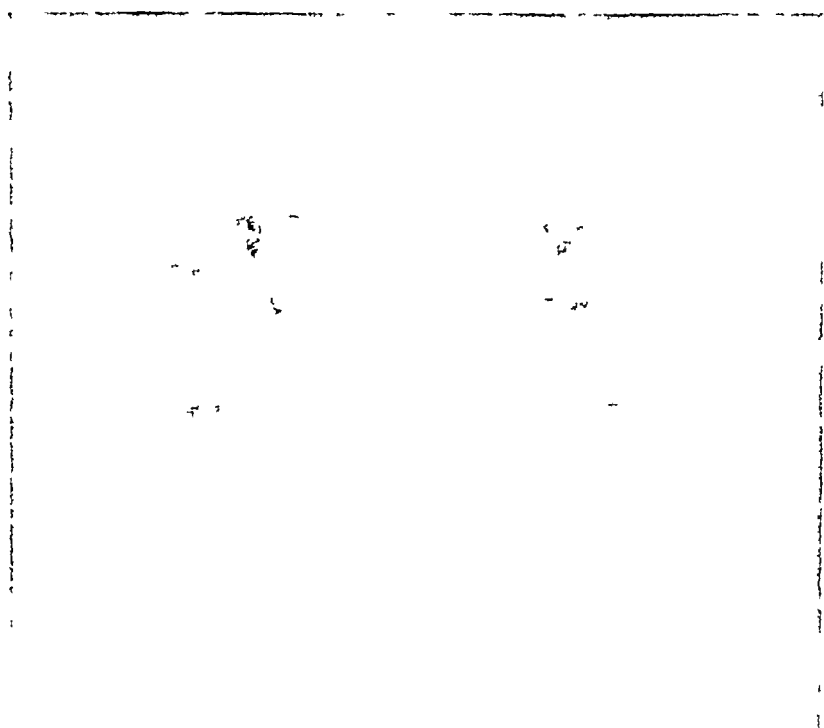


Fig 150—Roentgenogram of a 44 year old man with multiple pulmonary infarcts originating in a thrombophlebitis of the leg veins The onset has been sudden with pleural pain in the right chest while the patient was working Subsequently he complained of bilateral pleural pain and dyspnea

three weeks, though large lesions may persist for months with little change—

While the commonest circumstances under which the physician should look for evidences of thrombo-embolic disease are those in which patients are confined to bed for a period of time for whatever reason, there is another group of patients in which the disease apparently arises solely as a result of thrombophilic tendencies while the patient is ambulatory The importance of this group of cases of pulmonary embolism has been recently emphasized by Hampton, Pran

doni and King.⁷⁸ The onset of the disease is insidious or simulates coronary occlusion, pneumonia, angina pectoris or pericardial effusion. Usually dyspnea is more prominent than pain as a symptom. A chest x-ray of a patient which illustrates this condition is reproduced in Figure 150.

Electrocardiographic Changes in Pulmonary Embolism—In those cases of pulmonary embolism in which there is sufficient interference with pulmonary circulation to result in the production of right heart strain (acute cor pulmonale) dramatic changes in the electrocardiogram are often seen. McGinn and White⁷⁹ in 1935 emphasized the importance of a Q-wave and late inversion of T in Lead III, a rather low origin of the T wave with a gradual staircase ascent of the S-T interval in Lead II, a prominent S wave and slightly low origin of the T in Lead I, and an abnormal T in Lead IV. Such changes in the standard leads simulate those seen in infarction of the diaphragmatic surface of the heart (the so-called Q_sT_s type of electrocardiogram), but McGinn and White believed that Lead IV would serve to differentiate these conditions, since T_4 is usually normal in the latter. Barnes⁸⁰ was similarly impressed with the importance of Lead IV and stressed the diagnostic significance of the large S_1 in pulmonary embolism, a deflection usually absent, or very small, in the T_s type of electrocardiogram of myocardial infarction. Others^{81 82 83 84} have shown the frequency with which the changes described occur in pulmonary embolism and have confirmed their diagnostic value.

More recently⁸⁵ it has been shown that if electrocardiograms are taken within a short time of the embolic accident, and at intervals thereafter a series of changes with rapid evolution is demonstrated, and these may be summarized as follows:

Early Changes—(1) Intraventricular block of the right bundle branch type, with a broad, shallow S wave in Leads I and II, (2) marked depression of the S-T segment in Leads I and II may occasionally be present.

Later Changes—(1) Reestablishment of normal intraventricular conduction associated with the supplanting of the broad S wave in Leads I and II by a wave of sharp narrow contour, (2) a sloping ascent of the S-T segment in Leads I and II and (3) a Q wave and inverted T wave in Lead III. These changes are those described by McGinn and White.

Subsequent Changes—A disappearance of these changes by a gradual reversion toward the normal, except for the persistence in some of the changes in Lead III.

Lead IV, as originally reported by McGinn and White and by Barnes, has been supplanted in medical practice by exploratory chest leads, the exploring electrode being paired with an indifferent electrode. These leads have shown that the T waves are likely to be in-

verted in the leads from the right side of the precordium, but they may be normal in the CF_4 and CF_5 positions. These leads have also confirmed the impression that the early broad S_1 type of electrocardiogram of the standard leads is actually that of right bundle branch block since the intrinsic deflection is late in leads from the right side of the precordium and early in leads from the left side.

The electrocardiographic changes observed in pulmonary embolism are due, probably, to ischemia of the right ventricular musculature resulting from diminished coronary flow. The ischemia which is observed in the experimental animal with sudden marked distention of the right ventricle is located in an area just to the right, and only to the right, of the anterior descending branch of the left coronary artery, indicating that increased ventricular cavity pressure is an extremely important factor.³⁶

TREATMENT OF THROMBOEMBOLIC DISEASE

The ideal treatment is obviously prevention. Only by means of successful prophylactic measures can we ever hope to prevent the tragic sudden deaths which occur postoperatively and postpartum, a tragedy often heightened by the seemingly uneventful recovery of the patient before the moment of the calamitous crash. There is yet much to be learned concerning prevention, especially as regards the control of increased clotting tendencies, but much progress has been made in recent years and application of present known measures is effective in saving many lives and preventing much disability.

Prevention of Phlebotrombosis—Success is largely dependent upon the elimination, as much as possible, of the factors which may be etiologically important. Hines³⁷ has listed some of the means of accomplishing this in the postoperative patient, and his methods would be applicable also postpartum. He stresses, first, the importance of careful surgical technic with avoidance of trauma to tissue and especially to blood vessels. Abdominal compression is to be avoided by not using tight compresses and bandages which might interfere with venous return. Adequate fluid intake is important in the prevention of dehydration and consequent increased blood viscosity. Anemia must be corrected and infection promptly treated. Warm environmental temperatures should be provided, especially for the lower extremities. Respiratory and leg exercises and massage are important in favoring venous return and avoiding stagnation of blood in the extremities and abdominal veins. Finally, keeping the patient in bed for as short a period of time as is possible is extremely important and is a principle which is more and more widely recognized among surgeons. As has been pointed out by Robertson,³⁸ "No pulmonary embolism has ever resulted from getting out of bed too soon, although interns and nurses have been repeatedly made scapegoats in the scramble of attendants

to escape responsibility after an embolic death." Some surgeons have reported excellent results obtained by getting patients out of bed on the first postoperative day. Whether such an extreme in the application of the early rising principle is actually necessary is for the future to determine.

Anticoagulant Therapy—Therapy with anticoagulants has been used to abort the phlebothrombotic process and to prevent its extension and diminish the hazard of embolism when thrombosis has already occurred. Two anticoagulant agents have been extensively studied as to their potentialities and relative merits. The first of these, heparin, is normally produced in the body by the mast cells of Ehrlich, which are found chiefly in the vicinity of the finer blood vessels and especially concentrated in the capsule of the liver, the lung and the subcutaneous tissues.³⁹ This anticoagulant acts in at least two ways. First, it retards the rate of conversion of prothrombin to thrombin to an extent which is inversely proportional to the amount of thrombokinase present. Second, it reduces the effectiveness of the thrombin formed. Heparin and thrombokinase are direct antagonists; coagulation being prevented unless thrombokinase is predominant. Dicumarol, on the other hand, is thought by most investigators to exert a specific action in the reduction of the prothrombin content of the blood, although Dyckerhoff⁴⁰ holds that its anticoagulant effect is obtained through incapacitation of thrombokinase and does not enter into the second phase of clotting.

Heparin—Heparin may be administered by continuous intravenous drip by intermittent intravenous or intramuscular injection or by subcutaneous injection of heparin incorporated in the Pitkin menstruum. The last named method was introduced recently by Loewe and his co-workers⁴¹ and in their hands has proved to be a safe, simple, practical and effective method for the conservative treatment of venous thrombo-embolic disease. It appears possible that this method will replace all the others previously used because of its greater convenience and simplicity. The Pitkin menstruum heparin formula when combined with vasoconstrictor drugs results in great prolongation of absorption after subcutaneous injection. A dosage of 300 mg. is sufficient to heparinize the average individual, and this state may be maintained by a similar injection every other day. The effect of the heparin is judged by and based on determination of the blood coagulation time done at least once a day during the period of heparinization. In the clinical experience of the originators of this method no instance of pulmonary embolism has occurred in the presence of adequate treatment.

The intermittent intravenous method of heparin administration has been used by Bauer⁴² in a large series of cases, intensive therapy being instituted immediately after the diagnosis of thrombosis (or of pulmonary embolism) has been made. He used venography for the early

diagnosis of thrombotic disease. In comparison with material treated in the old, conservative way, heparin resulted in reducing the mortality to less than one-tenth and in lowering the time of confinement to bed from the previously customary forty days to about five days.

Dicumarol—Dicumarol has an advantage over heparin in that it is effective by oral administration and is far less expensive. Several days, however, usually elapse after the commencement of therapy before adequate anticoagulant action is achieved, whereas the effect of heparin is obtained within a few hours. Moreover, dicumarol is a more dangerous drug since its effects are prolonged and difficult to control if they become excessive. Its use is contraindicated in cases with hepatic damage, in those having a hemorrhagic diathesis, and in those with an already lowered prothrombin time. The dosage must always be carefully regulated by daily determinations of the prothrombin time, and the therapeutic level is reached when this is within 25 to 50 per cent of normal. The prolonged blood coagulation time after dicumarol therapy may be returned to normal in from three and one-half to thirty-six hours by the intravenous administration of large amounts (0.5 to 3.0 gm.) of vitamin K₁ oxide.⁴² It is possible, however, for a patient to die of hemorrhage before such therapy can be instituted.

Barker has reported on the use of dicumarol postoperatively for 624 patients at the Mayo Clinic.⁴³ In this group of patients there were 111 who survived pulmonary embolism or infarction before dicumarol was started. In only two of these did subsequent thrombosis occur, and in both there was apparently an inadequate elevation of the prothrombin time. When dicumarol was given to eighty-three patients with postoperative thrombophlebitis, further extension of the disease occurred in two, but there were no embolic accidents. Thrombosis or embolism did not occur in a group of 259 patients who had had abdominal hysterectomies and received prophylactic dicumarol postoperatively. In another group of 171 patients who were treated prophylactically because of a potential tendency to thrombo-embolic disease there was likewise no instance of thrombosis or embolism.

Surgical Prevention of Embolism—The surgical approach to the prevention of embolism was initiated in this country by Homans.⁴⁴ This approach attempts to place a block between the cardiopulmonary apparatus and the source of thrombi by ligation of involved veins. Unilateral superficial femoral vein ligation was the earliest operation used. In the few years in which this procedure has been practiced, however, it has become apparent that fatal pulmonary emboli may derive from an unsuspected thrombotic process on the contralateral side. Therefore bilateral superficial femoral vein ligation has become a common procedure in some clinics. A. W. Allen and his co-workers⁴⁵ report only 5 per cent subsequent sublethal emboli, and no fatal accidents after 579 femoral vein ligations. There are, however, known fa-

talities in which the embolus originated in the profunda femoris proximal to the site of ligation. Because of this Homans⁴⁵ has advocated common iliac and even inferior vena cava ligation. Two indications have been proposed for the latter ⁴⁶ (1) Concurrent phlebothrombosis in both lower extremities which has extended to or above the inguinal ligament, and (2) cases in which pulmonary embolism has occurred the source of which is not evident.

In contrast to the enthusiasm displayed by some for the surgical procedures, there are others who are equally strong in their opposition to their use. Hines³⁷ is of the opinion that ligation and division of the femoral and iliac veins and thrombectomy are less safe and more conducive to chronic venous insufficiency than is adequate and properly controlled anticoagulant therapy. Allen⁴⁷ states that venous thrombosis is not stopped by ligation of a vein, at best a pulmonary embolism is prevented from originating in a distal part of the occluded vessel. In his experience pulmonary embolism occurred in eleven of 202 patients after ligation of the femoral veins. Among another group of thirty nine patients pulmonary embolism resulted after ligation of peripheral veins in nine, three of whom died.

TREATMENT OF PULMONARY EMBOLISM

The occurrence of pulmonary embolism demands immediate application of emergency measures. Papaverine 0.03 gm ($\frac{1}{2}$ grain) and atropine 0.001 gm ($\frac{1}{100}$ grain) should be administered intravenously. These drugs tend to overcome the harmful reflexes which play an important role in the manifestations of the disease. When cyanosis and dyspnea are prominent symptoms oxygen should be administered in large amounts either by tent or, preferably, as 100 per cent oxygen by mask. Morphine may be used for relief of pain, but there is some danger of a harmful effect from suppression of respiration with large doses.

When a patient has recovered from an episode of pulmonary embolism, there is considerable danger that another may occur. DeTakats and Jesser² have estimated that a patient who has survived one pulmonary embolus has a 40 per cent chance of having a second embolic accident. It is therefore important to institute anticoagulant measures at once in any patient who has had an embolic accident and to continue this treatment properly controlled, until all manifestations of thrombo-embolic disease have disappeared and the patient is ambulatory.

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THE CHOICE AND METHOD OF ADMINISTRATION OF DIGITALIS GLYCOSIDE PREPARATIONS

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MANY years ago the famed Viennese physician, Wenckebach, said the following "Digitalis treatment is one of the most important and serious duties of the general physician, it demands a great deal of skill, power of observation, keen interest and experience a long life is too short to learn enough about this wonderful drug" This statement is probably more true today than it was a generation ago and the problem has only been complicated by the isolation and purification of the many cardio active glycosides found in digitalis purpurea, digitalis lanata and other plants The introduction of a host of cardioactive glycoside preparations derived from digitalis, squill and strophanthus with special trade names and a variety of dosages for oral and parenteral use has further confused the issue for the average physician

In general it can be said that the isolation of the cardioactive glycosides and the preparation of the various glycoside preparations by the pharmaceutical houses have rendered the medical profession a distinct service It is also true that the many products now available are reliable and effective when used correctly The fact remains however, that much confusion still exists in the field of digitalis therapy (In this discussion the terms "digitalis and digitalis therapy" will frequently be used in the broad sense to denote digitalis and all types of cardioactive glycosides)

There are many questions which may be asked regarding the use of digitalis and the cardioactive glycoside preparations What preparation is best for general use and how is it best given? What preparation is best for cardiac emergencies? When is parenteral use indicated? Should different preparations be given together (i.e., strophanthus and digitalis)? What preparations act most rapidly by mouth? Parenterally? What preparations are least toxic? Will other drugs be effective when digitalis fails? How is the digitalizing dose and maintenance dose best determined? It is with the hope of answering questions of this type and perhaps clarifying the subject somewhat that this topic is chosen for discussion

THE CARDIOACTIVE GLYCOSIDES

It is of interest that the many cardioactive glycosides which have been isolated are all from plant sources They occur in a variety of flora

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and are found in different parts of the various plants Table 1 lists the sources of a number of these glycosides The medicinal value of several of these has been known for centuries Those products derived from

TABLE 1 —ORIGIN OF CARDIOACTIVE GLYCOSIDES

<i>Digitalis</i> (Leaves)	<i>Squill</i> (Bulb)
A <i>Digitalis purpurea</i>	Scillaren A
1 Digitoxin	Scillaren B
2 Gitoxin	
3 Gitalin	<i>Strophanthus</i> (Seed)
B <i>Digitalis lanata</i>	Ouabain (gratus)
1 Digitanid A	Strophanthin K (kombe)
2 Digitanid B	
3 Digitanid C	<i>Thevetia nerifolia</i> (Nut)
	Thevetin
<i>Oleander</i>	
Oleandrin	<i>Periploca graeca</i> (Bark)
	Periplocin
<i>Lily of the Valley</i> (Flower)	
Convallamarin	

digitalis purpurea, *digitalis lanata*, *strophanthus* and *squill* are the best known Table 2 lists a number of the preparations in common use which are obtained from these plants

TABLE 2 —ORIGIN OF COMMONLY USED PREPARATIONS*

<i>Digitalis purpurea</i>	<i>Digitalis lanata</i>
Digitalis leaves	Digitanid
(a) Tablets, capsules or pills	Cedilanid (Lanotoside C)
(b) Tincture	
Digitan	Digoxin
Digiten	<i>Squill</i>
Digitolin	Scillaren
Digitoxin	Urginin
(a) Digitaline nativele	<i>Strophanthus</i>
(b) Purodigin	Ouabain (G)
(c) Crystodigin	Strophanthin K
Gitalin	

* No attempt has been made to include all preparations which are available

The qualitative action of these various glycosides seems to be identical Quantitatively, however, there is considerable difference in their action As pointed out by Gold,³ the quantitative differences are primarily in the following speed of action, duration of action, extent of absorption and potency It is important to understand all of these fac-

tors in order to appreciate the great variation in dosage which exists between the different glycosides when given orally. Thus, strophanthus preparations are so poorly absorbed that they are ineffective when given orally while the most potent of the digitalis glycosides, digitoxin is so completely absorbed from the gastrointestinal tract that the oral and parenteral dosage is the same. Between these two extremes lie the other cardioactive glycosides in extent of absorption. Table 3 sum-

TABLE 3—THE ACTION OF CARDIOACTIVE GLYCOSIDES

<i>Qualitatively</i>	Actions seem identical		
<i>Quantitatively</i>	Actions variable from quantitative standpoint		
(1) Extent of absorption	(2) Speed of action	(3) Potency	(4) Duration of action

EXTENT OF ORAL ABSORPTION IN MAN

Strophanthin	None	Whole leaf preparations	20%
Squill preparations	5%	Digoxin	20%
Cedilanid	10%	Digitoxin	100%
Whole leaf	20%		

marizes the action of the cardioactive glycosides and the relative extent of absorption of some of the more frequently used preparations. The figures on the oral absorption are derived from many sources. It should be stressed that they are approximate only and probably subject to some revision as further clinical studies are made. It is the opinion of the author that whole leaf preparations (those containing all of the glycosides in "purified" form) are more than 20 per cent absorbed. There is probably less variation in speed of action than was formerly supposed if the preparations are used in equivalent dosage. However, the strophanthus preparations probably act slightly more rapidly than the other glycosides when given intravenously. The duration of action is again a most variable thing, with strophanthus being the most transient (two to three days), while digitoxin (and whole leaf digitalis) show effects for as long as three weeks in some patients.

The determination of potency and standardization of the various glycosides was first done by bio-assay on animals. It was soon learned however that the actual dosage for man could be determined only by clinical trial of the glycosides on humans. This was based on the great variation in absorbability from the intestinal tract. As Sir Thomas Lewis said, "The proof or disproof of a drug's efficacy rests finally on the test in patients." Evidence has been gradually accumulating over the past two decades as to the potency and oral dosage of these glycosides. At present many of the glycosides which are isolated in pure form can be assayed entirely by weight, bio-assay being unnecessary. This is obviously a great step forward. The cat unit dosage of the

various glycosides and of digitalis itself is of academic interest, but for determination of the comparative oral dosage in man it is useless and misleading, and has added considerably to the confusion in dosage of the various drugs. Thus 1 mg of ouabain is equivalent to 10 cat units, and 1 mg of digitoxin is about 3 cat units, whereas 100 mg of digitalis leaves equals only 1 cat unit. The comparative doses of some of the glycosides and their approximate duration is summarized in Table 4.

TABLE 4—COMPARATIVE DOSAGE OF PURIFIED GLYCOSIDES

Preparation	Intravenous Digitalizing Dose, Mg	Oral Digitalizing Dose, Mg	Daily Dose, Mg	Duration of Action, Days
Strophanthin	0.5 to 1.0	Not effective	0.25-0.5	2-3
Squill	0.5 to 1.0	15-30	1.0	4-5
Cedilanid	1.0 to 2.0	10-20	1.0	7-10
Digoxin	1.0 to 2.0	4-8	0.5	5-7
Digitoxin	1.2 to 2.0	1.2-2.0	0.1-0.2	14-21

The qualitative action of the various cardioactive glycosides, as mentioned, seems to be identical and similar to that of whole leaf digitalis when given in adequate dosage. The most important and primary effect is a direct effect on the cardiac muscle fibers. There is increased force of systolic contraction with the ventricle emptying more completely, a shortening of systole and an increased filling time. The mechanical efficiency of the heart is increased with an increase in cardiac output and a decrease in the size of the heart in diastole. Reduction in venous pressure is probably accompanied by an increased coronary flow. Secondary slowing of the heart usually occurs. A less important action of the cardioactive glycosides is the effect on the cardiac rate as the result of their action on the conduction system. With therapeutic doses there is little or no direct effect on the pacemaker of the heart. Conduction in the auriculoventricular bundle is affected by decreasing the rate of conduction and increasing the refractory period. Reflex vagal effect is much less important than was once believed. These latter are effective mainly in slowing the ventricle in auricular fibrillation.

INDICATIONS AND CONTRAINDICATIONS

A detailed discussion as to indications and contraindications for digitalis therapy is not within the province of this article. However, there are a number of facts concerning this subject which are of great practical importance in the treatment of patients. They are not new, many of them being known to Withering, but they need reemphasis.

for all of those who deal with this type of therapy Luten, in his excellent book on digitalis,⁴ has included many of these under the term "Therapeutic Theses"

"There are a few, if any, situations in which digitalis is known to be of value *except heart failure* In almost all other situations it is of no value; in many it is harmful"

Digitalis is of value in the treatment of heart failure no matter what the heart rate may be rapid or slow Digitalis is of value in the earlier phases of heart failure shortness of breath cough, nocturnal dyspnea and rales at the bases are benefited and indicate its use, as well as congestive failure

High blood pressure low blood pressure, angina pectoris and chronic valvular disease are neither indications nor contraindications for digitalis therapy If failure is present the drug will usually help

Tachycardia per se is not an indication for digitalis therapy Toxic states, pneumonia, fever, septicemia, shock, hyperthyroidism and other similar conditions do not call for the drug It may do harm in such conditions

"The increase in output from the action of digitalis in the failing heart is effected without increase in work Digitalis lessens the energy requirement of the failing myocardium it does not force it to work harder but enables it to work better"

The most spectacular effects of digitalis therapy are seen in patients with auricular fibrillation with rapid ventricular rates and heart failure

There are many factors which influence the digitalizing dose for a given patient The age of the patient is important, older individuals taking relatively less of the drug The weight of the patient is of much less importance than was once thought and is of little practical value The degree of failure may be a factor and the amount of cardiac damage is also important

The more severely damaged the heart, the less the margin of safety between therapeutic and toxic doses "Certain patients with heart failure cannot be benefited by digitalis administration" (toxic effects appear before beneficial effects)

The most serious toxic effects are disturbances in cardiac rhythm Ventricular premature contractions and coupling of premature beats are frequent, auriculoventricular heart block, auricular fibrillation and ventricular tachycardia are less frequent but more serious manifestations. Ventricular fibrillation may occur from digitalis toxicity Any of these toxic manifestations may, and frequently do occur without nausea or vomiting.

The various cardioactive glycoside preparations are additive and cumulative and are not logically used together When toxic effects appear with one preparation other preparations will seldom prove beneficial to the patient.

Cardioactive drugs must be used with great care in patients who have recently been digitalized or who have had unknown amounts of digitalis

METHOD OF ADMINISTRATION

Despite the great tendency today to give medications by parenteral routes and notwithstanding the large number of glycoside preparations which can be given by these routes, the fact remains that 95 per cent of patients are best treated by oral medication. I feel that parenteral use of these drugs should be limited to real cardiac emergencies or the rare case in which medication cannot be given by the gastrointestinal route. Subcutaneous use is never indicated and the intramuscular route is often unreliable. As a group, these preparations are irritating and poorly absorbed, and with a failing circulation such medication must be given intravenously if a favorable result is to be expected.

There has been a great deal of abuse in the subcutaneous and intramuscular use of small doses of glycoside preparations, especially "purified" digitalis tinctures. It has been nearly a routine on many hospital services, both medical and surgical, to give such preparations to patients in circulatory collapse, shock and toxemias, and to moribund patients. This type of "medical last rites" must be eliminated with the more intelligent management of shock, circulatory failure, disturbed fluid balance, anoxemia and similar conditions. In the words of Luten, "Under the highest standards of practice the absence of an indication must be regarded as a contraindication."

There are occasional patients in whom the parenteral use of a glycoside preparation may be a life-saving measure. While such patients are not frequent, it is well to recognize the indications for such therapy and to be familiar with one or two preparations suitable for such administration. One of the primary indications for intravenous therapy with cardioactive glycosides is *pulmonary edema* due to acute left ventricular failure. Other methods of treatment (morphine, oxygen, diuretics, and so forth) should be utilized and morphine in full doses is probably the most valuable single measure. Oxygen is frequently not available immediately, and intravenous digitalis therapy should be considered. It may be combined with aminophylline and even a mercurial diuretic may be added. Auricular fibrillation with rapid ventricular rate and severe cardiac failure may be an indication for such therapy and occasionally patients with normal sinus rhythm and extreme failure are desirable candidates, especially if vomiting is present from a congested liver and gastrointestinal tract. It should be stressed that such patients are infrequent but they are seen in the admitting wards of city hospitals and occasionally in general practice, under unusual circumstances. If death appears imminent (within two to three hours) it seems logical that only medicine given by the intravenous route could be effective.

CHOICE OF PREPARATIONS

It is well established that the action of all of the cardioactive glycosides is qualitatively similar no matter what their origin. If this is true, there is no real advantage of one over the other in so far as real action on the failing heart is concerned. It may be an advantage, of course at times, to use a preparation which acts more quickly due to more rapid absorption. The variation in duration of action as the result of more rapid elimination or destruction of the glycoside might occasionally have some bearing on the individual problem. However, prolonged action is desired in practically every cardiac patient and severe toxic effects can usually be avoided, so that rapid elimination of the glycoside is probably of questionable importance. The most rapidly eliminated glycosides, the strophanthins, cannot be given orally and their action is so transient (two to three days) that they are of no value for routine use. The use of strophanthus (parenterally) combined with digitalis (orally) has been advocated in the treatment of congestive heart failure.¹ The advantages of such a combination are certainly questionable, and the evidences of toxicity at the end of twenty-four hours were unusually high in the series reported. In a clinical study extending over several years, Stroud, Vander Veer and others^{7, 8, 9} followed a considerable group of patients with cardiac failure. The failures were of varied etiology but mainly the patients had rheumatic heart disease and auricular fibrillation. They were maintained for periods of about a year each, on digitalis leaves, a preparation containing all of the glycosides of digitalis purpurea, digitoxin, gitalin digoxin and a squill glycoside preparation. Digitalizing doses and relative maintenance doses were determined clinically. There was no essential difference in results with the various preparations if they were used in adequate dosage. None was less toxic or more effective than the others. In several patients with severely damaged hearts in whom toxic effects (usually coupling of premature beats) appeared before adequate clinical improvement was manifest, the same toxic symptoms resulted with the use of other glycosides. It was the opinion of the authors that whole leaf digitalis was as satisfactory as any of the glycoside preparations and probably the drug of choice for routine use.

A change from one preparation is occasionally desirable for various reasons. If patients have experienced toxic effects especially nausea and vomiting, on one preparation, they may refuse to continue the drug. In such cases, switching to another product of different appearance may be helpful. It should be remembered that the new drug should be continued in maintenance dosage only if the patient is digitalized. The difference in rapidity of absorption of the various glycosides is so slight as to be of doubtful clinical significance when given orally.

With the recent work of Gold and his associates, demonstrating the

complete absorption of digitoxin when given orally and the possibility of digitalizing a patient with a single oral dose of this drug, there has been a great campaign by the pharmaceutical companies to popularize this glycoside and the one-dose method of digitalization. In a considerable experience with this drug a decade ago, and in recent studies on well controlled patients with cardiac failure, I have found preparations of this glycoside much less "fool-proof" than would be gathered from the articles in the literature or the advertisements in the current medical journals. It is certainly one of the most important of the cardio-active glycosides and the work of Gold and his collaborators has been an excellent contribution to our knowledge of digitalis and digitalis therapy. It is true that the advocated dose of 1.2 mg of digitoxin can usually be tolerated and is usually a safe dose if the patient has received no other digitalis preparation, but this does not necessarily prove that it is a wise procedure for routine use in digitalizing patients. If anything, it is too simplified. There is no substitute for a thorough knowledge of the action of digitalis preparations including beneficial and toxic effects, and experience with their use in treating patients. It is very likely that toxic effects and failures with digitoxin will be as frequent as with other preparations in the hands of the inexperienced. The advocated maintenance dose of digitoxin (0.2 mg) is slightly larger than is well tolerated by the average patient. It is true that some patients who are shifted from a maintenance dose of 0.1 gm ($1\frac{1}{2}$ grains) of standardized digitalis leaves to 0.2 mg of digitoxin are improved. This is due to giving more of the active glycoside and the same result will be obtained in this type of patient, in whom an insufficient maintenance dose was being given, by increasing the dose of digitalis.

The choice of preparation for emergency use is not a difficult one. The method of administration and the dosage employed are of more importance than the actual preparation employed. It is more important to know thoroughly the action and the dosage of one or two preparations than to have a smattering of knowledge of a number of them. It is believed that intravenous use is always desirable when feasible, and it is seldom that this cannot be accomplished. When this is impossible, intramuscular use should be resorted to, but never subcutaneous administration.

In a review of the emergency cases in which glycoside preparations were used at the Pennsylvania Hospital during a ten year period, Vander Veer and Wagner¹⁰ found that a "purified" tincture containing all of the glycoside purpurea (digalen) was very satisfactory when used intravenously in adequate dosage. A further detailed study was made on one patient with rapid auricular fibrillation (rheumatic heart disease with mitral stenosis) who was voluntarily hospitalized for several months. Numerous glycoside preparations of digitalis purpurea

digitalis lanata, *strophanthus* and squill were used intravenously as the patient developed heart failure on successive occasions. The rate and degree of improvement was measured by the venous pressure, circulation time and reduction in heart rate, as well as subjective improvement. It was found that the action of all of the glycosides was identical, with little if any difference in the rapidity of action, when used in adequate dosage. The duration of action was extremely variable. No advantage could be seen with the *strophanthus* preparations over the *digitalis* glycosides, and the squill glycosides were equally as rapid and effective in this study. It is realized that this comparison of the results in only one patient is not conclusive, but it represents an opportunity seldom afforded under controlled conditions.

Strophanthus preparations are frequently advocated for emergency cardiac use. They are potent drugs, but it is doubtful if they act significantly faster than some of the *digitalis* glycosides and they have the disadvantage of losing their potency with time (a factor in a drug used infrequently). Their short duration of action may be a disadvantage as well as an advantage when they are combined with other preparations that must be utilized to control the patient.

The *digitalis* glycosides, when used separately or in combination in the "purified" tinctures are effective and rapid in action if used intravenously. Digoxin, cedilanid (lanatoside C), the squill preparations and the various glycoside combinations (digalen, digifolin, digilanid, etc.) are all satisfactory preparations when used in correct dosage. It must be stressed that the dosage of the many preparations varies greatly and that the dosage for the individual product he is using for emergency use must be known by the physician.

DIGITALIZING, MAINTENANCE AND EMERGENCY DOSAGE

Stated briefly, the dose of *digitalis* or any of the cardioactive glycosides is enough and not too much. This fact was well known to Withering and was stressed in his classic, "An Account of the Foxglove" (1785). The actual approximate digitalizing and maintenance doses of the many cardioactive preparations has been determined entirely by clinical trial on patients. By the same token, the actual digitalizing dose and maintenance dose for any one patient must be determined individually. There is no relation of the "cat unit" dose of any one of these preparations to the others when given orally, because of the great variation in absorbability from the gastrointestinal tract. For this reason the approximate digitalizing dose of a given preparation must be known to the physician. There are no shortcuts to good digitalis therapy.

The approximate oral digitalizing dose for *digitalis* leaves and the various glycoside preparations is known. For *digitalis* this is from 1 to 2 gm (15 to 30 grains) depending on the individual patient and

how rapidly the medication is given. In the average case the full dose can be safely given in forty-eight to seventy-two hours when the patient is under fairly close observation. The more severely ill the patient, the more closely he must be observed. In these patients, rapid digitalization is often desirable, so toxic effects must be carefully watched for. For the average patient a practical plan is as follows. An initial dose of 0.4 gm (6 grains) is given followed by 0.2 gm (3 grains) three times daily, or every six hours. When the dose reaches the neighborhood of 1.2 gm (18 grains) the dose is cut to 0.1 gm (1½ grains) three times daily. At the sign of improvement the medication is reduced to 0.1 gm daily. When toxic signs or symptoms precede beneficial effects, the medicine must be stopped at once.

The most frequent maintenance dose of digitalis leaves is 0.1 gm daily, approximately 60 per cent of patients being maintained on this amount. However, more or less than this amount is frequently desirable. The *optimum* maintenance dose must be determined by trial on the individual patient. It is not the average maintenance dose. Neither is it necessarily the maximum amount tolerated or the minimum effective dose. Thus a patient may be more comfortable and better controlled on six or eight tablets per week than on seven. A simple plan to accomplish this is to omit the Sunday dose or to give a double dose on Sunday. The use of two tablets one day and one the following day, alternately, is often a satisfactory method in those needing dosage well above 0.1 gm per day. Occasional patients will tolerate as much as 0.2 gm per day, but this is seldom an optimum dose. Digitalis tincture is not recommended for routine use. It is less stable than the leaves, but more important, the dosage is less accurate and there is a frequent tendency on the part of the patient to "adjust" his own dose to suit his symptoms.

The average oral digitalizing dose for a few glycoside preparations is given in Table 4. The digitalizing dose is usually presented in the literature accompanying the various products and a plan similar to that outline can be followed for any of the glycosides. A useful plan for digitalizing patients who are borderline cases—the so-called "therapeutic trial" case, is to put the patient on 0.1 gm of digitalis, or similar dose of a glycoside preparation, three times daily for a week. This type of patient can be safely allowed to go this length of time without observation as he is not apt to develop severe toxic manifestations. At the end of this time if the patient is definitely improved he can be placed on a maintenance dose, or the medicine can be discontinued.

The single dose method of digitalization with digitoxin, as advocated by Gold and collaborators, has already been discussed briefly. It is probably a safe method for most patients, but in those seriously ill it is apt to be unsatisfactory. I have seen several instances of poor results

under this regimen They were not the fault of the glycoside, but resulted from following the "method" rather than following the patient It is difficult to improve upon the principle of frequently repeated small doses with careful observation of their effects on the sick patient, continuing the drug until beneficial or minor toxic effects are evident Remember, the more seriously damaged the heart, the more the patient needs digitalis, but the less the margin of safety between beneficial and toxic effects

In cardiac emergencies, the *intravenous* use of a cardioactive glycoside preparation is recommended Ouabain, strophanthin K, cedilanid, digoxin and the "purified" tinctures (digalen, digilanid) will give equally good results if given in adequate dosage and will produce toxic effects if given in overdosage or to those who have been receiving digitalis In our experience there is no significant advantage of one preparation over another if they are given intravenously in equivalent dosage. The possible exception is digitoxin which apparently acts more slowly than the other glycosides, and has seldom been advocated for emergency use. We have seldom used strophanthus preparations for the reasons previously given in this article. The important thing for the average physician is to know the dosage of one or two reliable preparations and to have them available for immediate use if the emergency arises.

In a busy receiving ward and associated cardiac ward service, we have found the intravenous use of the purified tincture containing all of the glycosides of digitalis (digalen) very satisfactory in emergency cases which are undoubtedly cardiac, and in which it is certain that no digitalis has been taken prior to admission An initial dose of 4 cat units is given very slowly (undiluted) intravenously This may be repeated in one to two hours if the patient is not improved More often a second dose of 2 cat units is given in three to four hours Digitalis is started orally as soon as the patient can take it. A total dose of 8 to 12 cat units is occasionally given in divided doses, over several hours

Digoxin and cedilanid are both very effective given intravenously A total dose of about 1 mg. of either can be given over a few hours, giving about half the dose initially and judging the subsequent doses by the response of the patient.

It should be stressed again that cardiac emergencies requiring intravenous glycoside therapy are infrequent and that other measures known to be of value (morphine oxygen, diuretics, and the like) should be utilized in this type of patient.

SUMMARY

1. Cardioactive glycosides are widely distributed in nature
2. The action of all is qualitatively similar
3. Considerable variation exists in the degree of absorption, potency,

duration of action, and to a lesser extent, the speed of action of the various glycosides

4 None of the substances seems to be more potent but less toxic than the others

5 Under certain conditions it may be desirable to use glucoside preparations rather than whole leaf digitalis or tincture of digitalis

6 There are a number of preparations satisfactory for intravenous use in cardiac emergencies Their action is quite similar if used in equivalent dosage

7 It is desirable to have a working knowledge of one or two cardio-active glycoside preparations, but it is more important to be thoroughly familiar with the indications, contraindications, beneficial and toxic effects of digitalis itself There are no shortcuts to good digitalis therapy, clinical experience plus careful observation of the patient are most essential in the proper treatment of the seriously ill cardiac patient

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THE TREATMENT OF CORONARY DISEASE

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THE following paper will sketch our general plan of management for two of the commonest and most important problems in coronary artery disease (1) the attack of coronary occlusion and (2) angina of effort with a more or less stabilized coronary circulation

THE TREATMENT OF A PATIENT WITH AN ATTACK OF CORONARY OCCLUSION

In the treatment of the attack of acute coronary occlusion it is helpful as a preliminary step to attempt to fit the patient into his proper position in a "severity scale" Such a severity scale might be outlined as follows

(a) *Severe* Severe prolonged pain shock, tachycardia, fever leukocytosis and signs of cardiac insufficiency (dyspnea, cyanosis, pulmonary edema and basal rales)

(b) *Moderately Severe* Pain, electrocardiographic signs, fever and leukocytosis without signs of cardiac insufficiency

(c) *Mild*. Pain, electrocardiographic changes, no fever, no leukocytosis no cardiac insufficiency

(d) *Very Mild*. Brief pain (five to twenty minutes), no other signs except that, from this time on, angina of effort will occur, or if previously present, will be more easily produced (In this instance one must visualize the occlusion of an artery with such good collateral circulation that an actual infarct does not occur as a result, there is an area of myocardium with a precarious blood supply which becomes ischemic only during exercise.)

Treatment of the Severe Attack -1 Bed rest It is not easy or wise to be dogmatic about the length of time a patient should remain in bed after a severe attack. Bed rest will probably average four to six weeks. In general, a patient is allowed out of bed in a chair three weeks after fever leukocytosis, severe pain and circulatory failure have disappeared. No walking is allowed until the sedimentation rate has returned to its pre attack level (see below) and until the electrocardiogram has stopped changing.

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2 For pain, give *morphine* in sufficient amounts to control the intense pain, but not enough to depress respirations below 12 per minute. Start with 15 mg intravenously and repeat in fifteen minutes if necessary. Intravenous injection is indicated because of slow absorption from subcutaneous injection in a shocked patient and the possibility of dangerous cumulative effects coming on if several subcutaneous injections are later absorbed simultaneously.

3 *Oxygen* may help the pain and is indicated for cyanosis and dyspnea. The blister type of head cover, face mask and nasal catheter are the order of preference.

4 To prevent an intraventricular clot with subsequent embolus, *dicumarol* has been used.¹ It may be valuable, but it is a relatively new method of treatment and has not been assessed completely. Before making it a routine procedure its dangers must be balanced against its possible advantages. *Dicumarol* might also be useful as a prophylactic against phlebothrombosis if it is found to be safe.

5 To dilate coronary vessels *papaverine*, 0.1 gm four times a day, has been suggested.² It may help. We have occasionally seen syncope follow its use. *Theophylline ethylenediamine*, 0.1 to 0.3 gm three times a day (m) may be useful. It may also upset the stomach. Five-tenths gram of this drug in 200 cc of physiological salt solution given slowly over a period of one hour as an intravenous drip may help to relieve pain and improve the circulation but should not be used routinely.

6 *Barbiturates*. After the most acute part of the attack is over phenobarbital, 30 mg three times a day, is often useful to control apprehension and nervousness. *Seconal*, 0.1 gm, as a nocturnal sedative is usually well borne.

7 *Digitalis* is usually contraindicated. It should be avoided in the first few days. After the first week it may be tried cautiously if dyspnea persists or tends to increase. Never digitalize the patient rapidly. Even in the face of a paroxysm of auricular fibrillation, *digitalis* should usually be withheld unless congestive phenomena appear to be endangering the patient's life. This advice is based on the fact that the paroxysms of auricular fibrillation which occur in the first two weeks after coronary occlusion usually subside within twenty-four hours or less without producing major circulatory failure. Moreover, sudden death during digitalization occurs frequently enough in patients with acute cardiac infarction to suggest cause and effect.

8 *Quinidine* has been suggested as a prophylactic against ventricular fibrillation. In our experience it has not proved definitely valuable. We do not use it routinely in arrhythmias except paroxysmal ventricular tachycardia. Then it should be administered in adequate doses. If 0.3 gm every second hour for five doses is ineffective, this dose may be doubled.

9 *Food.* Give the patient an 800 calorie diet with 60 gm of protein and 1 polyvitamin tablet daily. Divide the food into six small feedings. Never fill the stomach.

10 *Fluid.* Give the patient enough to keep him from being thirsty.

11 *Bowels.* After the first day or two, if bowels are costive, give a small enema or a mild evening laxative. If the patient fights the bed pan, the actual amount of cardiac work incident to moving the bowels may be lessened by having two attendants support him sitting on the pan on the edge of the bed, or actually lift him on to a commode beside the bed. However, these deviations from usual procedure are to be used only when they are really indicated. Most patients become accustomed to using the bed pan after a few attempts. After the patient is allowed out of bed let him use a commode next to his chair until walking is permitted.

12 *Attending to business.* A man will rest better if you allow him to get things off his mind which are bothering him. His secretary or a partner may often be allowed access to him for brief periods. It is better in general not to allow use of the telephone.

13 *Tobacco.* Tobacco is contraindicated, at least until the acute stage is over.

14 *Coffee.* Its use is no more contraindicated than is aminophylline in a man who is used to it.

15 *Treatment of recurring attacks of pain.* In a few individuals, during convalescence, anginal attacks occur, which may be related to vasoconstriction of collateral coronary arteries. In such an event, nitroglycerin 0.2 mg. to 0.25 mg. under the tongue is worth trying. It has not, in our experience, caused a material drop of blood pressure, and has often terminated the pain. Amyl nitrite, which produces a more definite reduction of blood pressure, is probably contraindicated.

16 *Electrocardiography* is useful in diagnosing the infarct and in diagnosing arrhythmia should it appear. When the electrocardiogram becomes stable, this is often an indication that the acute process is sufficiently quiescent to allow the patient more freedom of movement, provided that other criteria mentioned above are consistent with this move.

17 *Erythrocyte sedimentation rate.* A study of a series of patients of the coronary age group attending our Cardiac Clinic, without known infection or active infarction, showed a rapid sedimentation rate in about 30 per cent. Therefore in order to make the best use of this test in acute coronary occlusion, it is helpful to know the patient's pre attack sedimentation rate or the rate in the first few hours after the attack, before it has had time to become accelerated by the infarct. After a severe cardiac infarction keep the patient in bed, or in a chair next to the bed until the erythrocyte sedimentation rate reaches nor

mal, if his pre-attack rate was normal. If previously abnormal or not known, the erythrocyte sedimentation rate may be misleading.

18 *What to tell the patient.* Avoid terms like "thrombosis," "blood clot" and "heart attack" which tend to cause apprehension. It is usually necessary, however, to tell him in a general way what has happened to him, as soon as his mental condition warrants it. It does no harm in most instances and helps to enlist his cooperation. Our usual plan is to say, "You have had an obstruction of one of the small arteries which nourish the muscle of your heart. It is like a broken leg, you must give it as complete rest as possible by being as quiet in body and mind as you can. You must not exert yourself physically or emotionally until healing occurs. If you do this the condition will tend to heal as a broken leg will heal." His next question is, usually, "Doctor, will I be a permanent invalid?" This may be answered, "If you knew the number of men in important positions in the world who have been through an attack like yours, you would be encouraged."

Treatment for the Moderately Severe Attack.—1 *Bed rest* will average three weeks. About two weeks after fever leukocytosis and pain have generally subsided, and the patient may be allowed in a chair next to the bed. The time to permit walking is judged on the same basis as after the severe attack.

2 *Morphine* is used subcutaneously, the initial dose being 15 mg. The attempt should be made to take the edge off suffering but not necessarily to relieve all pain, or the respiratory rate may be depressed too far. Give the patient enough at least to control restlessness and apprehension.

3 *Oxygen* may help control pain, even when cyanosis is not obvious. The rest of the therapy is much the same as for the severe attack.

Treatment of the Mild Attack.—1 *Bed rest.* Seven to ten days of bed rest usually suffice. Then the patient is permitted to be up in a chair. Walking is allowed on the same basis as after the severe attack.

2 *Morphine* is used as in the moderately severe attack.

3 *Oxygen* is rarely needed.

The rest of the therapy is based on principles outlined for the severe attack, except that barbiturates are not used so freely, the diet may be a little less restricted after the first few days, and the patient may be permitted more contacts with his business if it does not have an adverse effect upon him.

Treatment of the Very Mild Attack.—Patients who have experienced only a very mild attack need no bed rest, no morphine, none of the usual treatment for the acute attack. However, when angina of effort begins with evidence of a mild coronary episode, or when established angina suddenly changes its character suggesting a possible fresh occlusion, it is wise to confine the patient to his room and limit

exercise drastically for the time being, usually permitting only quiet walking around one room. The *diet* should be restricted somewhat and overfilling of the stomach should be avoided. *Papaverine* or *theophylline ethylenediamine* is prescribed, usually with small doses of barbiturates. *Nitroglycerin* is used for recurrences of pain (0.25 mg). Smoking is interdicted. Business contacts which do not irritate or excite the patient are allowed. After two weeks *exercise* is very gradually increased if it does not precipitate pain.

The patient with symptoms of a "very mild attack" is occasionally in considerable immediate danger. Instead of a small coronary artery being blocked completely, he may be experiencing the slow, progressive occlusion of a large artery. His symptoms may therefore be the prodromal phenomena of a very severe attack to come. Consequently they demand care and vigilance on the part of the physician. Their importance should never be minimized.

Management after the Acute Attack—At the end of a period of rest after acute coronary occlusion, the unstable patient will often confront the physician with a rather complex assortment of symptoms some of which are organic and some of which are induced or magnified by apprehension. This is one of the most delicate situations we are called upon to handle, and many errors have been made in each direction. The general rule is that after all objective evidences of an active process have subsided, it is more detrimental to the patient's future mental and physical health to treat all symptoms as dangerous signals than to begin to minimize some of them such as consciousness of cardiac action, sighing respiration, sharp pains here and there in the chest, especially at the apex, and tenderness of the chest wall. Never at any time should one minimize the importance of dull, constricting pain beneath the sternum coming on in relatively brief episodes and disappearing completely.

After an acute coronary occlusion, a small number of patients will continue to have recurring attacks of substernal pain at rest for some time, even for months. These attacks are often accompanied by the electrocardiographic signs of acute myocardial anoxemia. This type of pain should be regarded as an indication that a section of heart muscle still has a precarious blood supply. As long as it continues the patient should remain relatively quiet, under fairly strict supervision of his diet and habits. The pain should be treated with small doses of nitroglycerin or morphine. It is important to recognize that this clinical picture often tends to subside with the passage of time if the physician does not become impatient and advise heroic therapeutic measures, such as the removal of a gallbladder or the section of cervical sympathetics.

TREATMENT OF THE PATIENT WHO HAS ANGINA OF EFFORT WITH A MORE OR LESS STABILIZED CORONARY CIRCULATION

Before describing the treatment of this clinical picture it might be well to describe exactly what we mean by it. This type of patient may have had one or more large or small cardiac infarcts in the past. They can be recognized by inquiring about former attacks of chest pain, usually centering under the sternum, but not always thought of by the patient as having been cardiac attacks. The patient is asked in detail where he was, what he was doing, what time of day it was, who was there, etc. It will be found that, in the vast majority of attacks of coronary occlusion, the patient has a photographic memory of the surrounding circumstances, including a number of relatively unimportant accompanying incidents. Many other acute (noncardiac) attacks similarly photograph the environment in the patient's mind. However, when a patient gives a history of chest pain, a photographic memory of the episode favors the diagnosis of coronary occlusion, and the lack of a detailed recollection of the surrounding circumstances is a strong point against this diagnosis. After he has recovered from the attack, the patient will have recurring episodes of discomfort in the chest, usually under the sternum. These attacks come on during exertion, especially after eating, while outdoors walking against a cold wind. They stop within a few minutes when he stops exerting. He usually stands still and looks in a store window if he is on the street. If a chair is near he will sit down. He will prefer to stand or sit rather than to lie down. The pain is not necessarily severe, it is dull, aching, constricting, pressing, squeezing or burning. It is very rarely sharp. It does not throb. It often "goes up to my throat and chokes me." The patient may even deny that it is a "pain." One of the helpful diagnostic points is that when the patient is first^{*} asked "What sort of a pain is it, and where is it?" he will raise both hands in front of his chest, stop a moment to think, then with a slightly puzzled look (because the pain is difficult to describe) he will put both hands on his upper or middle chest to either side of the sternum. A fairly reliable rule is that, if a patient places one hand at the apex, the pain is not likely to be angina of effort, if he shows you a midline or bilaterally symmetrical location with both hands, it is angina until proved otherwise.

Finally, it should be stressed that angina of effort is diagnosed by the history. There may be no electrocardiographic abnormalities. There usually are no abnormalities on physical examination of the heart which assist in the diagnosis.

Given a patient with this clinical picture, who has had substernal pain on effort for a number of months, and who has noted no recent

* After he has been asked this question a number of times his response often becomes more glib and less characteristic.

dramatic change in the amount of effort which will produce it, it is proper to diagnose "angina of effort with a more or less stable coronary circulation."

Treatment.—1. The first step as a rule is to *describe to the patient what the situation is from the standpoint of pathologic physiology*, unless there is a compelling reason why this should not be done "You have a small artery going to a section of the muscle of your heart which is slightly narrowed. While you are at rest, enough blood gets through the narrowed artery to nourish that section of heart muscle. When you exercise beyond a certain point and increase the work of the heart, that part of the heart muscle needs more blood than will flow through the narrowed artery. When it gets insufficient blood supply for the work it has to do, you feel pain in your chest. If you stop exerting yourself as soon as you feel the pain, you notice it will pass off rapidly."

2. *Induce the patient to stay within his exercise tolerance*, and to live in such a way as not to bring on the pain. Discuss in detail the precipitating factors, (a) exertion such as walking rapidly up hill, up a flight of stairs, against a cold wind, carrying a bag (b) the effect of eating before exertion, especially overfilling the stomach, (c) the effect of hurrying and rushing, of emotional tension or anger. Ask him if there are any particular acts or combinations of circumstances which he knows will bring on his pain and advise him to abstain from them. "If you get up fifteen minutes earlier and read the paper fifteen minutes after breakfast, you may find that you can walk to the station comfortably after that."

3. *Look for, and treat removable conditions which are contributing to the myocardial anoxemia during exercise* (a) Excess weight. "You are carrying around a 30 pound suitcase wherever you go. If you can get rid of that suitcase you will be able to exercise much more freely without producing pain." If you give him an incentive to reduce, and then give him a 1000 calorie diet the results may be very gratifying. (b) Anemia. (c) Hyperthyroidism. It is our practice to advise total thyroidectomy in patients with angina and hyperthyroidism. Results may be dramatic. Beware of using thyroid substance in patients with angina of effort. If it is used, it must be given with great circumspection because it often increases angina of effort.

4. It is usually worth while to try the effect of "coronary vasodilators" but without too much confidence in their efficacy. "I want you to take these pills (theophylline ethylenediamine, 0.1 to 0.2 gm) three times a day after meals. In some people they help to dilate the arteries in the heart. Try them and see if they have this effect on you. You will know if they have, by the fact that your pain will come on less readily." Sometimes phenobarbital 15 to 30 mg may be combined with

each dose of theophylline ethylenediamine with favorable results, especially in a high-strung individual

5 *Nitrites* If you give nitroglycerin to every patient with angina of effort and tell him to take a pill whenever he has a pain he may well come back the next time with the following story "Did the pills help to stop your pain?" "I don't know, the pain stops right away when I stop walking, so I couldn't tell." Consequently, in patients with mild pain which stops promptly when exertion is stopped, nitroglycerin may not be necessary. The drug is used most frequently to stop severe attacks which will not subside spontaneously. However, it is most helpful in the patient who cannot do some necessary act of his life without producing pain. If he cannot get to the station on a cold winter morning without anginal pain, give him 0.20 to 0.25 mg of nitroglycerin to take two or three minutes before he starts. If he cannot have a bowel movement without pain, have him take nitroglycerin a few minutes before he goes to stool. It is not helpful to give a patient nitroglycerin on schedule, three or four times a day. It merely induces tolerance to the drug (which, however, is very temporary, lasting only a few days). It is unwise to start nitroglycerin at a higher dose than 0.20 to 0.25 mg because these small doses will often be effective whereas a larger dose may induce a throbbing headache. We often tell a patient to chew up the pill rather than to put it under the tongue, especially if there is necessity for keeping him from knowing he is taking nitroglycerin. It is absorbed just as well. We usually prescribe the hypodermic tablets since they dissolve more readily. Amyl nitrite is not as generally useful as nitroglycerin because the dose is more difficult to adjust so as to prevent a drop of blood pressure and throbbing headache. Moreover, it is less convenient to carry. Both these nitrites produce their effects promptly, within less than five minutes. If the pain for which they are given does not begin to subside until fifteen to twenty minutes after administration of the drug, its subsidence is probably not due to the drug.

6 *Tobacco* It is well to suggest stopping tobacco on the following basis "Smoking seems to have a definitely harmful effect on some people with this condition. If I had your condition, I would stop tobacco for six weeks and see if it made any difference. It is true that in some individuals tobacco does not seem to be harmful, but you cannot tell except by trying it out. If after giving it up for six weeks, you feel that you can do without it indefinitely, it would be wise for you to do so."

7 *Alcohol* "The only danger in drinking is that (a) If you have cocktails before dinner it may make you overeat at dinner, which is harmful. (b) If you drink too much, you may want to show the guests how you ran the hurdles in 1903. If it makes you overexert, it is harm-

ful. If you can drink temperately without producing either of these effects, it will do your condition no harm."

8 *Digitalis* is usually unnecessary and may be harmful in the treatment of the clinical picture outlined above.

9 *Epinephrine*, *ephedrine* and *pituirrin* often precipitate anginal attacks and should, in general, be avoided in all patients with coronary disease.

10 Operations on, or alcohol injections of, the cervicodorsal sympathetic nervous system are very rarely indicated because the pain can be controlled quite adequately in the vast majority of patients without resorting to such procedures. However, the occasional high strung patient with intense anginal pain which he cannot prevent because of his instability may receive real help from sympathetic nerve block. Other cardiac operations such as producing pericardial adhesions, ligating a coronary vein or sympathectomizing the coronary circulation are still in the class of experimental procedures whose value has not been demonstrated beyond doubt.

11 After giving the patient a number of precautionary and therapeutic measures, it is often wise to make an encouraging move "I want you to take regular *setting up exercises* in the morning before breakfast. It is quite possible that by giving your heart mild exercise without producing pain, you can help to increase the circulation and improve your condition. Take mild calisthenics. Find out how much you can do without pain. Be careful never to bring on the pain." This advice will often improve the patient's morale greatly. He will say to himself "If the doctor suggests I take exercise, I can't have a very bad heart." Dr. Lewis A. Connor originated this procedure in the treatment of angina of effort and it is often quite useful at least from the psychological standpoint.

12. *Prevention of the progress of the underlying disease* We do not know the cause of coronary atherosclerosis. We do not know what makes the disease progress rapidly in one patient and very slowly in another. If we observe a number of individuals with coronary disease over a period of years it is clear that the rate of progress of the disease is not strictly related to the care with which the various patients have followed the routine advice which physicians are apt to give them. Consequently one is not justified in demanding dogmatically that the patient give up his work, his physical activity and the various vices which make his life tolerable. Most men are happier if permitted to "live their life."

In respect to exercise, we may say to the patient "You should give up strenuous physical exercise, tennis, heavy lifting and the like because in some cases such strains seem to precipitate trouble. You may play golf if you enjoy the game, provided that you can do it without

inducing pain in your chest This usually requires that you play on a fairly level course with relaxing companions, and at a peaceful tempo"

Although as mentioned we advise against excessive smoking, it is not our practice to battle the habit with religious fervor

We do not at present stress the importance of a low cholesterol diet unless the patient has a high level of blood cholesterol

Regarding vocational activities it is well to suggest something like the following "Patients seem to do better, as a rule, if they get out of the wild hurly-burly of competitive business life Yet many of them do badly if they retire completely Unload some of your harassing work on your subordinates Take life a little more leisurely and enjoy it Avoid tension as much as you can Get on an even keel Keep your job, if you can do it under these terms Get to the office a little later, leave a little earlier Get a rest after lunch and a good sleep every night. When you feel that life is getting you on the run, stay away from work for a few days and get out of its clutches" Of course, many patients cannot achieve this utopia for temperamental or economic reasons, yet it is probably well for them to attempt to plan their lives along these lines If a patient wants to retire, we do not advise him against it, but suggest that he consider whether he has enough internal resources to avoid boredom and a feeling of futility in retirement

13 The final step is to ask the patient, "*Do you have any questions you wish to ask me?*" Then you will hear one or more of the following, which may be answered as follows

Question "Do I have angina?"

Answer "Angina is a term which was invented over a hundred and fifty years ago Some years ago a French physician described several score of conditions to which this name had been applied Some of them are diseases which have captured the popular imagination because of their dramatic or painful features You don't have severe pain You can control it as I have outlined I have given you a description of the way your pain comes about. That is what you have, call it what you will"

Question "Is there danger of sudden death?"

Answer "Let's consider the various dangers that surround you and put this one in its proper perspective You drove to town today There was danger of an accident which might have maimed or killed you You knew this, yet it did not oppress you or make you apprehensive or unhappy If you run a mile it may kill you If you bring on the pain by injudicious activity and don't stop what you are doing the moment you feel the pain, you are doing a dangerous thing If you abide by rules and live within your exercise tolerance, I expect you to do very well Under these circumstances, the danger of your condition is not much greater than the other dangers you encounter in your daily life"

Question "How long will I live and should I make a will?"

Answer "Everyone with any property should have a will. Many patients with this condition live for years and live very useful lives."

Question "Will I get better?"

Answer "If you avoid exercising to the point of producing pain, it may become harder and harder to bring it on. The pain may even subside completely with the passage of time, as the arteries in the neighborhood of the narrow vessel increase their ability to carry blood."

When a man first develops coronary disease he is apt to be afraid—a new danger has come over his horizon. In the course of time, however, he becomes accustomed to it and does not experience so much mental suffering. It is our duty to help him through the first stage of the new fear as wisely and gently as we can and to point out to him from the very beginning that he may well be rehabilitated and lead a long and useful life. His life may be less active physically but it may also be less turbulent, consequently it may actually be a happier existence than that which he was forced to relinquish.

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DIET AND DIURETICS IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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DIET and diuretics have always been an important part of the treatment of congestive heart failure. The treatment of this disorder has not changed materially since William Withering first described how digitalis should be used. We have progressed in our understanding of congestive failure and of the effect of the methods we use in treating it. However, our aims and therapies remain about the same. Rest, sedation, digitalis, diets and diuretics are used very much as they were 150 years ago. We have new and better diuretics, to be sure, and we know more about food than we used to. We know a great deal more about the water and electrolyte metabolism of the body, and it is probably in this field of water balance that the greatest advance in our understanding of heart failure has been made. Diet and diuretics are both closely associated with the water and electrolyte balance of the patient in congestive heart failure and for that reason they are discussed together in this paper.

DIET

Attention to diet has received tremendous impetus in recent years with our increased knowledge of the various properties of food. This is no less true in heart disease than in other disorders. The selection of a proper diet in a cardiac patient can make the difference between invalidism and "good function." Long ago, Sir William Osler said, "The stomach is not only a near, but a bad neighbor of the heart."¹ One hesitates to go so far as that, for after all, the heart owes much to the stomach. The heart must have all the essential food elements to work efficiently. However, it is well to remember that a full stomach means work for the heart. During digestion and assimilation of food, cardiac output may increase 30 per cent, and this increase in heart work may last two to four hours after the food has been taken.² Furthermore, gastric distention and flatulence may embarrass the heart in its work, either by upward pressure on the diaphragm, or through the gastrocardiac syndrome.³ Obesity, the result of too much food, in direct proportion to its amount, will increase the work of the heart.⁴ Malnutrition, so common in persons with long-standing heart disease, because of the inadequate intake of essential food elements as vital for the heart as any other organ, puts the heart, already labored with

disease, under further disadvantage. Therefore, in the selection of a diet for the cardiac patient, one must consider each case, his state of nutrition and the functional capacity of his heart. In the hospital little difficulty will arise in procuring the desired diet. In the home it is important to survey the patient's economic status, his eating habits, how he obtains food and how it is cooked. One must be sure that the patient is able to carry out the instructions given him.

In the acute stage of congestive heart failure, the patient is usually not interested in food and the problem of calories need not concern one for the first two or three days. Edema and passive congestion involve the stomach and intestines, and handicap their function. The symptoms of anorexia, nausea, distention and flatulence indicate that the intestines are not functioning well. These patients cannot cope with much food and it should not be forced upon them. It is best to begin with liquids. The Karell diet⁵ of 200 cc. of skimmed milk four times a day may be all the patient can tolerate. It has the advantage of being low in salt (about 1 gm.) and in calories (328) and its assimilation will place little or no burden on the heart. Other liquids or gruels may be substituted for milk, for example the whites of six to ten eggs flavored with lemon, milk with lime juice, whey, thin cereal gruels and cream soups. Dry biscuits, zwieback and toast may be added if the patient wants more. Salted biscuits, salted broths and citrus fruit juices should be given with care if at all for they have a high sodium content. This regimen should be continued for no more than two to three days as it is vitally deficient in minerals, vitamins and calories.

In two or three days, or as soon as the patient can tolerate it, the diet should be increased. Most patients when seen in congestive failure can tolerate some food. A few, even after three or four days on the liquid regimen described above, may continue to suffer from extreme anorexia. Then the ingenuity of the doctor and nurses must be called upon to maintain nutrition. Tube feedings and even parontral feedings may be necessary. The majority of patients, however, are able and anxious to eat after twelve to twenty four hours of liquids. In general, it is wise to begin with a light diet and increase the amounts until the food is adequate to maintain normal weight. Such a maintenance diet is approximately 2000 calories for most adults with heart disease (Table 1).⁷ It is best to make up the bulk of the food with carbohydrates, giving around 250 gm. and to limit the proteins to the minimum amount consistent with bodily requirements. This amount of protein has been found to be close to 50 gm. for most adults (1 gm. per kilogram of body weight). Fats are added averaging about 100 gm., to make up the remainder of the diet. Ideally, the selection of foods should be left to the patient in so far as possible and it is interesting to note how often they will select the foods that are consid-

TABLE 1 —CARDIAC DIET, WEIGHT AND APPROXIMATED MEASUREMENTS*†

MEALS			LUNCHES		
Breakfast	Grams	Measure	9 A.M.	Grams	Measure
Milk	100	$\frac{1}{2}$ cup	Water	100	$\frac{1}{2}$ cup
Cream	66	$\frac{1}{4}$ cup	or Crushed ice	100	1 cup
Cereal (cooked)	120	$\frac{1}{2}$ cup			
Sucrose	10	$\frac{2}{3}$ tsp	10 A.M.		
Glucose	10	3 tsp	Orange juice	150	$\frac{3}{4}$ cup
Dextrine-Maltose	10	3 tsp	Lemon juice	5	1 tsp
			Glucose	20	6 tsp
Dinner					
Soup { Cream	132	$\frac{1}{2}$ cup	3 P.M.		
{ Potato	50	$\frac{1}{2}$ cup	Milk	100	$\frac{1}{4}$ cup
{ Butter	10	2 tsp	Cream		$\frac{1}{4}$ cup
Ice cream	100	$\frac{1}{4}$ cup	Flavoring		
or Junket‡		$\frac{1}{2}$ cup	Dextrine-maltose	12	4 tsp
Milk	100	$\frac{1}{2}$ cup	Sucrose	5	1 tsp
Water	100	$\frac{1}{2}$ cup			
or Crushed ice	100	1 cup			
Supper			4 P.M.		
Soup { Cream	66	$\frac{1}{4}$ cup	Water	100	$\frac{1}{2}$ cup
{ Milk	100	$\frac{1}{2}$ cup	or Crushed ice	100	1 cup
{ Spinach§	50	$\frac{1}{4}$ cup			
Butter	10	2 tsp			
Custard { Egg	50	1 egg	7 P.M.		
{ Milk	100	$\frac{1}{2}$ cup	Milk	150	$\frac{1}{4}$ cup
{ Lactose	10	3 tsp	Dextrine-maltose	10	3 tsp
{ Glucose	10	3 tsp	or Candy		1 stick

* Smith, F. M., Gibson, R. B. and Ross, N. G. Diet in the Treatment of Cardiac Failure J.A.M.A., 88 1943 (June 8) 1927

† The composition of the weighed diet (calculated) is protein, 44 gm., carbohydrate, 220.6 gm., fat, 109 gm., and calories, 2076. Additions to the diet are made between the fourth and the tenth day, beginning with toast, jelly, salt-free crackers, and butter, sieved fruit and baked potato are included later. If the diet is first increased on the fourth day, the patient may be receiving as final additions to the basic diet protein, 37 gm., carbohydrate, 112.3 gm., fat, 25 gm., and calories, 718, as follows: breakfast, toast, 20 gm., butter, 10 gm., jelly, 20 gm., dinner, baked potato, 1, sieved fruit juice, 100 gm., toast, 20 gm., butter, 10 gm., supper, sieved fruit, 100 gm., toast, 20 gm., butter, 10 gm. Stick candy may be substituted anywhere in the diet for the equivalent amount of sugar.

‡ Milk, 100 gm., cream, 66 gm., sucrose, 5 gm., dextrine-maltose, 10 gm., and a half junket tablet. When junket is served, the milk at 7 P.M. is reduced to 100 gm.

§ Puréed spinach. Other vegetables may be substituted.

best for them. These are the simple and easily digested foods, such as cooked cereals with sugar and cream, biscuits, toast with unsalted butter, eggs, white meat of chicken, vegetable purées, jellies, custards, junkets and ice cream. The average hospital "soft, low salt diet" or "cardiac" diet is adequate and will serve the purpose in most cases. In the home, these foods are easily prepared and there should be little

trouble with the diet, provided the physician gives the proper instructions on preparation (see section on intake of sodium chloride below) Foods which produce flatulence should be avoided. These include the cabbage family, the onion family, the bean family, melons, raw apples, concentrated sweets, carbonated beverages, and highly seasoned foods Large meals tend to produce distention and embarrass the heart. Small meals with intermediate feedings are better tolerated, especially by the patients with severe cardiac embarrassment.

Malnutrition is common in persons with chronic heart disease in whom anorexia has led to an inadequate diet over a long period of time Total serum protein values between 5.5 and 6 gm are frequent findings, particularly when edema is present The cause of this mild degree of hypoproteinemia is probably not entirely due to faulty nutrition Albumin loss into the urine and into the edema fluid, dilution of serum proteins by increased blood volume and impaired liver function may all be factors behind the lowered serum protein⁵ In most patients with these findings there is a return to a normal level when the edema disappears and the diets already described are adequate for their nutrition For patients with mild to moderate degrees of malnutrition who require more food, it is best to increase the carbohydrate content of the diet up to 300 or 400 gm Diets of around 3000 calories, high in carbohydrate, are easily assimilated and will generally add enough to the nutrition of these patients to meet their requirements In the few cases with severe grades of malnutrition, an increase of the protein of the diet may be indicated. These may be the very patients who suffer most from anorexia and are therefore the most difficult to feed. Today there are many valuable concentrated protein products available and, with these, it is not too difficult to increase the protein intake in the poorest eaters up to 100 or even 150 gm. a day Some of these products contain sodium chloride and should be used with caution. Dried milk (casein) is a valuable protein product, free of sodium chloride. It may be added to milk and soups which provides an excellent means for increasing a patient's protein consumption.

Careful attention should be given to vitamins in any prescribed diet. Since most of these patients are restricted in the amounts and kinds of food they can eat, it is probably wise to supplement their food with one of the preparations that contain maintenance doses of all the vitamins. Varying degrees of vitamin deficiencies are commonly associated with malnutrition Of all the vitamins thiamine is the most intimately connected with the heart. "Beriberi heart" is a clinical entity recognized today in all manuals on cardiology^{6, 7} A constant supply of this vitamin is necessary for optimum nutrition because of the limited capacity of the body to store it. Thiamine deficiency, as a primary cause of heart failure, is not common It may, however, be a factor in impaired cardiac function when malnutrition is a complication of the

commoner types of heart disease. It is always wise therefore to include it in the diet of a patient in congestive failure. A therapeutic dose of 10 mg of thiamine hydrochloride a day is sufficient in the average case. If a severe degree of deficiency is suspected, then 50 mg, or more, will be necessary. The other vitamins must not be neglected. Given in the form of multivitamin preparations, they are usually supplied in sufficient quantities. Greater amounts can be given in the concentrated forms when indicated.

Once the cardiac patient is over his attack of congestive failure and is up and about again, his diet can be liberalized. However, he should be restrained from overeating and from eating too much at one time, and he should try to keep his weight 5 to 10 pounds below the normal for his height and age. Obesity is a needless hardship for any patient with heart disease. Overweight patients should be put on a limited diet and their weight allowed to fall gradually to normal limits or a little below. The benefits derived from loss of weight are definite and have been demonstrated by Master and his associates.⁴ They showed that a loss of from 12 to 15 per cent in body weight of obese patients was accompanied by as much as 35 per cent reduction in cardiac work. The importance of this decrease in work is obvious in the overweight patient with heart disease.

WATER AND SODIUM CHLORIDE

Regulation of water and sodium chloride in the diet is of great importance in any program for the treatment of heart failure. Heart failure, whether it be an acute or a gradual process, interferes markedly with the fluid and electrolyte dynamics of the body. One of the results of this interference is the accumulation of these elements in the extracellular tissue spaces. This accumulation reveals itself as increased body weight and edema. The primary cause of this process is naturally failure of the heart. The sequence of events which leads to edema is not clear even today. Kidney function definitely falls off with the onset of failure as evidenced by oliguria and diminished output of sodium chloride.^{9, 10} Nitrogen retention is also common, and that it is not always due to kidney disease is shown by the frequency with which it disappears along with the edema. One of the goals in the treatment of congestive failure is to rid the body of edema. Its very presence implies increased blood volume, swollen extracellular tissue spaces, increased body weight and tissue anoxia, all of which add to the difficulties of a diseased heart. Composed almost entirely of electrolytes and water, edema fluid must be eliminated through the kidneys. Kidney function thus must be reestablished and maintained. The water and sodium chloride in a patient's diet are both of great importance in this process.

The subject of water consumption in the presence of edema has long interested clinicians. The custom, until recently, has been to limit fluids

whenever there was congestive heart failure. The assumption was that the ingestion of more than limited amounts of fluid would increase the edema and, furthermore, that if fluid ingestion was limited the body would draw on the water in the tissue spaces for urine formation, a diuresis would be promoted and the edema would subside. Actually neither of these assumptions appears to be correct in the light of our present knowledge. It has been reported many times in the past and recently demonstrated in the laboratory that edema will not be increased by water alone unless the edema fluids are dehydrated.¹¹ The body's fluids are primarily of salt and water, and in health or disease the body is extremely sensitive to any change in their tonicity. An increase in these fluids can only occur with water and electrolytes together. The sodium salts in isotonic solution with water can and do diffuse freely into all the extracellular spaces. In health the body is able to keep the amount of its fluids and electrolytes within certain bounds and to rid itself promptly of an excess of either through the kidney. The regulating ability is lost during heart failure, and edema is the physical sign of a large increase of the body fluids. This increase occurs only when the proper materials are available. There must be sodium salts available to accompany the water into the tissue spaces. Water alone will dilute the body fluids and, though the body may lose the ability to regulate the quantity of fluids in the tissue spaces, it continues to retain its ability to regulate the quality of its fluids within close bounds. Loss of this function would mean death. Therefore, excess water, even when the kidneys are diseased, is promptly unloaded in the urine. That this process occurs during heart failure has been demonstrated by Schroeder,¹¹ by Proger and associates¹² and by Schemm.^{13, 14, 15} All of these investigators gave large amounts of water to cardiac patients on restricted salt diets, without producing an increase in their edema.

The kidneys must have sufficient water to function properly. There must be enough water available to act as a vehicle for the products of metabolism which are filtered from the blood by the kidneys and passed out in the urine. Healthy kidneys are able to concentrate these products in urine and thus economize on water. They usually require about a liter of water every day to rid the body of the products of metabolism which are constantly being formed. Diseased kidneys lose the power to concentrate and may require 2 liters or more to do the same job. Water reaches the kidneys only after the other demands of the body are met. If the available water is too little, then the kidneys cannot clear the blood of metabolites as they should and these products accumulate in the blood and tissues. Just such a process occurs in the untreated cardiac patient who is developing edema, not because he is drinking less water than usual—he may be drinking more—but because what water he is drinking is diffusing into his tissue spaces along with

the sodium he is ingesting His body has lost the ability to control the quantities of its interstitial fluids As a result, too little water is left over for the kidneys to make urine What little urine is excreted is as concentrated as the kidneys can make it, thus indicating that they are doing the best they can Dehydration is common in these patients even though their tissue fluids may be swollen to many times the normal amount¹³ Sweating is one important factor responsible for this dehydration, for through it much water is lost without electrolytes Furthermore, as long as these electrolytes stay in the tissue spaces, they will hold water as their solvent Water will not be released until the body begins to unload the electrolytes into the urine in the process of diuresis Limiting water by itself will not promote diuresis but rather dehydration and oliguria Thirst, dry red tongue and loss of tissue turgor are all signs of the need for water, and they are very common in the patient with acute congestive heart failure These patients crave water, and what better indication is there that the body needs water than thirst?

Generally it is a good practice to let patients drink as much water as they desire Some will drink up to 4 and 5 liters daily No harm will come from this even in the most edematous patients, provided sodium salts are properly restricted (See section on sodium chloride below) The amount of fluid a patient needs can be judged by his urinary output Intake and output should always be watched in a cardiac patient If his output stays over 1200 cc a day, then as a rule he is drinking enough to maintain adequate elimination of metabolites He probably is not, however, getting rid of any accumulated salts and water from his tissues If his output falls below 1000 cc, he is not drinking enough and he should be encouraged to take more One of the basic aims in the treatment of congestive heart failure is to help the body rid itself of edema A diuresis is the sign that the body is unloading its excess fluids and electrolytes Urine volume gives information about kidney function and the presence or absence of a diuresis Only the patient's weight will tell accurately of the gain or loss of edema, and it is most helpful to follow it at regular intervals Schemm has pointed out recently, as others have before him, that water will act as a diuretic when given in sufficient amounts and when the sodium of the diet is controlled^{13 14 15} He says, "Less than enough water leads to dehydration Any reasonable amount more than enough, does no harm"¹³ In fact, he believes in pushing the water intake of these patients up to 4000 cc and even 8000 cc, depending on the hydration of the patient and provided the sodium in the diet is properly controlled Such a program in his hands has often led to diuresis and loss of edema without the help of diuretics However, it takes courage to push water in an edematous patient and it is not generally necessary to give the large amounts which Schemm advo-

cates. An intake of around 2500 cc. in conjunction with restriction of sodium chloride, with rest, digitalis and diuretics is usually adequate for the treatment of these patients

As has been said before, edema cannot develop unless the elements that make up the tissue fluids are available. Water without sodium ions will not increase edema. Sodium salts make up the bulk of the electrolytes. Therefore, it is obvious that the supply of these salts should be curtailed. Time and again it has been shown that edema waxes and wanes in direct proportion to the sodium in the diet. Schroeder, in an excellent study,¹¹ showed that when the sodium chloride of the diet was kept around 1 gm a day, edema decreased in cardiac patients regardless of the fluid intake, and when the sodium chloride was increased to 5 to 6 gm a day, the edema increased. During the period when edema is developing in the cardiac patient, for reasons not yet explained, the output of sodium chloride in the urine diminishes below the patient's intake. In the healthy individual the intake and output of sodium salts tend to balance one another from day to day. When the intake of sodium is unrestricted in the cardiac patient, an excess of these salts accumulate in the body, and in solution they diffuse freely into the tissue spaces to swell the edema. Therefore, one's aim should be to reduce the intake of sodium chloride to equal the output, or less. The sodium chloride in the average American diet amounts to 10 to 15 gm. a day. The greatest part of this is added by the cook or the individual as table salt. By eliminating table salt from a person's food when it is cooked and when it is eaten, the sodium chloride in his diet may be reduced to 3 or 4 gm a day. Most foods contain some sodium chloride and it is not possible nor desirable to eliminate it entirely from the diet. Some foods, however, contain greater amounts than others and by limiting these, further reductions in the amount of sodium salts ingested can be made.

For practical purposes, the following instructions will provide an adequate low salt diet for the average cardiac patient. His food should be cooked without the addition of salt and he should not add salt when he eats it. He should avoid all foods prepared with salt such as smoked or dried meats and fish, canned foods and especially canned vegetables, cheeses, salted biscuits and nuts, prepared seasonings such as chili sauce, catsup and German mustard, breads prepared with baking soda, salted broths and any soups cooked with salted pork. He should be warned not to use vegetable salts, sodium bicarbonate or any proprietary medicines for "gas" and indigestion. These all contain sodium as the primary basic ion. Calcium, magnesium and aluminum salts may be substituted to relieve indigestion. Milk contains about 1 gm. of sodium chloride per liter. It is a valuable food and should not be cut out of a diet, but rather limited to a liter a day including the amounts used in cooking. If these instructions are followed conscientiously

tiously the sodium chloride in the diet will be reduced from 10 gm to 2 or 3 gm a day For the average patient in congestive failure or subject to it, this is an adequate restriction of sodium chloride Should the food be unpalatable to him, plain mustard in water, vinegar and lemon drops will help season it A few patients with very severe heart disease may require a still greater reduction of their sodium intake before they can get rid of their edema Schroeder has described two diets extremely low in sodium, one with 1 gm a day, and the other with 0.5 gm,¹¹ and these may be helpful in the occasional resistant case

A most interesting dietary program for congestive heart failure has been developed recently by F. R. Schemm^{13 14 15} The principles upon which he based his program are, in general, similar to the ones presented so far in this paper However, he goes further in his analysis of the development and elimination of edema fluid He says, in effect, that the salts of edema fluid are primarily an alkaline mixture of five parts sodium chloride and one part sodium bicarbonate Sodium will leave the bicarbonate ions to form neutral salts with the strong acid ions such as are formed constantly by metabolism These neutral salts are promptly excreted by the kidneys The bicarbonate ions are eliminated by the lungs as carbon dioxide This reduction in the amount of sodium bicarbonate upsets the ratio of chloride to bicarbonate ions and tends to reduce the pH of the tissue fluids To avoid this, the body will unload in the urine a like amount of sodium chloride All of these electrolytes will carry water with them from the tissue spaces to the urine In such a way it is thought that the body unloads the excess electrolytes and water which have accumulated to form edema The aim of Schemm's regimen is to "(1) Decrease the ingestion of the material essential to the formation of edema and encourage the mobilization of sodium already retained by giving a diet restricted in sodium and yielding a neutral ash (2) Increase and hasten the normal effect of the metabolic acids by administration of small amounts of acid drugs (3) Facilitate the elimination of the mobilized sodium via the kidneys and avoid the development of true cellular dehydration by administering plain water in adequate amounts, i e., adequate according to water balance principles"¹³

Construction of a diet to meet these requirements is based on the fact that milk, vegetables and most fruits yield an alkaline ash, while meats, eggs and cereal foods yield an acid ash By balancing the intake of these two groups of foods, the total reaction of the diet can be regulated to yield a neutral or slightly acid ash Sodium salts are restricted in the diet in the same way as was described in a previous section However, the benefit of the diet is not as much based on a low sodium intake as on the intake of an excess of acid ions Tables 2 and 3 con-

tain the skeleton outline for neutral diets taken from Schemm's article and a sample of a neutral diet

TABLE 2—SKELETON OUTLINE FOR NEUTRAL DIETS¹¹

General Diet

Basic Ash Foods	Limited 24 hr maximum	Acid Ash Foods	No limit
Milk	1 pint	Eggs	24 hr maximum
Vegetables	2 servings	Meat, fish, fowl	2
Fruits	2 servings (except prune, plum, cranberry as desired)	Breads or cereals	1 serving
			5 slices or servings

TABLE 3—INITIAL NEUTRAL DIET

Six Small Feedings with Protein 60 to 70 gm. Calories 2400

Food	Measure	Food	Measure
1. Cereal and Cream		2. Eggnogg	
Cereal prepared or uncooked	$\frac{3}{4}$ cup	One egg	
or cooked	1 tbsp	Milk	$\frac{1}{2}$ cup
Cream (20%)	$\frac{1}{2}$ cup	Cream (20%)	$\frac{1}{2}$ cup
Sugar	$\frac{1}{2}$ cup	Sugar and spice	
	2 tbsp		
3. Fruit, Bread and Milk		4. Corn Soup	
Prunes	$\frac{1}{2}$ cup	Corn purée	$\frac{1}{2}$ cup
Bread	1 slice	Bread	1 slice
Butter	1 pat	Butter	1 pat
Milk	1 cup	Cream	$\frac{1}{2}$ cup
5. Eggs, Toast and Milk		6. Bread and Milk	
One egg		Milk	1 cup
Bread	1 slice	Cream (20%)	1 tbsp.
Butter	1 pat	Bread	2 slices
Milk	1 cup	Butter	1 tbsp
Cream	2 tbsp		

DIURETICS

Diuretics are drugs used to increase the volume of urine. As was said in a previous section, one of the primary aims in the treatment of congestive heart failure is to help the patient get rid of edema. Since

edema fluids must go out through the kidneys, any measure that will increase the volume output of the kidneys will be of value. Increased urine volume will occur when glomerular filtrate is increased and when there is diminished resorption of the glomerular filtrate by the tubules. All things which assist the heart to improve the circulation and thus the blood flow to the kidneys will favor a diuresis. It is well known that rest in bed frequently leads to a diuresis in a cardiac patient. Digitalis when first introduced by William Withering was thought to be a diuretic because a diuresis so often followed its use, though experience has taught that its effect is primarily in increasing the efficiency of the heart. The resorption of the glomerular filtrate by the tubules depends on the electrolyte composition of the filtrate and the amount of water the body can spare from the filtrate. The relation of water and sodium salts to edema fluids and kidney function has already been discussed. Suffice it to say that any increase in urine volume will depend to a large extent on a proper restriction of sodium chloride in the diet and ample ingestion of water. In fact, as mentioned, water given in sufficient amounts may by itself stimulate a diuresis, as has been shown by Schemm and others.¹⁴

There is a group of drugs whose primary effect is to increase urine volume. In general, they work by either increasing the glomerular filtrate or by decreasing the tubular resorption.^{16, 17} They are used in congestive heart failure to promote a diuresis, and thus to help the body get rid of its edema. Their effect depends on a certain amount of intact kidney parenchyma and on an adequate circulation, therefore they should be looked upon as supplementary to the other more fundamental forms of treatment. When a patient in congestive failure does not respond with a diuresis despite rest, digitalis, adequate fluid intake, and salt restriction, then one of these drugs is indicated. It will frequently cause a great increase in urine volume which leads to diminution of the edema, and often relief from many symptoms caused by it. Furthermore, diuretics may be of great value when given periodically to cardiac patients who are constantly on the verge of congestive failure by helping them keep free of edema and thus be more comfortable.

The *mercurials* are the most effective of the diuretics we have today. Mild mercurous chloride (calomel) has been used as a diuretic for many many years, but its action is uncertain and it is apt to cause toxic symptoms. In recent years more satisfactory mercury compounds have been introduced. Salyrgan and mereurophylline (mereupurin) (a mercury-theophylline compound) are possibly the two most widely used, and there is not much to choose between them. There is some evidence that theophylline combined with the mercurial adds to its diuretic effect and it is now possible to get a salyrgan-theophylline preparation.¹⁵ These drugs are most effective given intravenously, in 1 to 2 cc.

doses They may be given intramuscularly in the same dosage, but their action is slower and less certain, particularly in a very edematous patient. Care must be taken not to inject the drug subcutaneously or it will cause great pain and may lead to ulceration Toxic effects are rare, but do occur¹⁰ These fall into three groups (1) those associated with diuresis and due to dehydration, loss of chloride or both, such as weakness, apathy, delirium and muscle cramps, (2) those due to digitalis toxicity, when digitalis concentration in the blood is increased as a result of the loss of tissue fluids, and (3) those due to mercury, such as stomatitis, nausea, colitis, kidney irritation with casts, albumin and red cells, skin eruptions, chills and fever, and sudden death. Many hundreds of people have been given these drugs periodically for months or years without trouble and with great benefit. In the acutely decompensated patient they are best given three to four days after rest and digitalis have had a chance to work. Then, given intravenously, they may cause a huge diuresis and be of immense benefit to the patient. They may be repeated every four to five days until the edema disappears The patient's weight will afford the best index of the state of his edema, and by following it one can judge the effect, or the lack of effect, of the diuretic. During convalescence or indefinitely thereafter these drugs may be given periodically as often as once a week and are of great value in forestalling the accumulation of edema in those who are susceptible to it. Recently several clinics have reported giving both mercupurin and salyrgan theophylline by mouth.^{20 21} Given in one dose of five tablets or two tablets three times a day for two to four days, they will produce a satisfactory diuresis No severe toxic reactions have been reported, but nausea, vomiting and diarrhea do occur One to two tablets given daily for weeks at a time have been found of definite value in helping to ward off edema in one group of patients with severe heart disease for whom digitalis no longer maintained compensation.

Another widely used group of diuretics are the *xanthines* The effect of these drugs is thought to be mainly due to an increase of the glomerular filtrate, though there is some evidence that they diminish tubular resorption too.¹⁷ Perhaps their greatest use is found in the ambulant patient. Given daily their mild diuretic effect will often help to ward off the accumulation of edema. The greatest difficulty in their use has been the frequent occurrence of gastric irritation with anorexia, nausea and even vomiting. These effects have been diminished in some of the newer preparations Of the many xanthine drugs on the market only a few will be mentioned, namely theobromine sodium salicylate (diuretin) theobromine calcium salicylate (theocalcin) theobromine sodium acetate (thesodate) calcium theobromine and calcium gluconate (calpurate) The dosage for all is 0.5 to 1 gm three to four times a day for several days or weeks If effective they may be given

indefinitely, or in courses of seven to ten days at weekly or biweekly intervals. There is some evidence that the calcium salts of theobromine may be more effective and less irritating than the others.

Urea is another useful diuretic. It should not be given when there is elevation of the blood urea nitrogen. It is very soluble in water and its disagreeable taste may be hidden with lemon juice. Given in doses of 15 to 90 gm daily for three to five days it often causes a prompt and large diuresis. It may be repeated in five to seven days if necessary. Its effect is probably due to an increase of the solids in the glomerular filtrate. When they are eliminated in the urine, they tend to carry water with them.

The *acid-forming salts* are another widely used group of diuretic drugs. These include the ammonium, potassium, magnesium and calcium salts. Ammonium chloride is probably the most commonly used of the group. Given alone to the patient in congestive failure, they usually cause little more than a mild diuresis. Given in conjunction with a mercurial diuretic, they often augment the effect of the latter considerably.^{8 16} They are frequently given to the ambulant patient in courses of one to two weeks, or indefinitely in the hope that their effect may be of help in keeping him free of edema. In any event, their dosage is 1 gm four to six times a day. They are prone to cause indigestion and nausea, and for this reason may work more hardship than good on a patient. The reason for their diuretic effect is not entirely clear, though it is thought that because of their acidifying effects they are promptly unloaded into the urine where they tend to carry water with them.²²

To sum up, diuretic drugs are indicated in the treatment of congestive heart failure in order to speed up the elimination of edema fluid, and to help prevent the recurrence of this fluid. They should be used in conjunction with the other forms of treatment and not by themselves, because their effect is on the result of the disorder, and not on the cause. The actual diuretic employed will depend upon the results obtained in a given case. They all have their uses, and the physician will do well to familiarize himself with the various types.

SUMMARY

To summarize, diet and diuretics are important parts of the treatment of congestive heart disease. They were discussed together in this paper because of their close association with the fluid and electrolyte balance of the patient or, as we commonly express it, with his "intake and output." It is to be emphasized, however, that they are merely parts of the treatment of this disorder, and it is only as they are fitted into the whole scheme of therapy, which includes rest, oxygen, sedation and digitalis, that the patient will derive satisfactory results from

them. In fact, there is probably no other disorder in which the different elements of treatment are so dependent one on the other for success, as in congestive heart failure

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THE DIAGNOSIS AND MANAGEMENT OF CHRONIC VALVULAR HEART DISEASE

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ETIOLOGY AND PATHOLOGY

THE management of chronic valvular disease depends upon the proper diagnosis. Rheumatic fever, syphilis, atherosclerosis, infectious endocarditis and congenital abnormalities are responsible for almost all the damage. Rheumatic fever is by far the commonest cause and is more prevalent in colder climates. Syphilitic heart disease, usually secondary to aortitis, is preventable by adequate, early antiluetic therapy. Atherosclerotic changes occur as part of the aging process while infectious endocarditis in most instances attacks only previously damaged heart valves and, strangely enough, often those with the slightest pathologic change are involved.

The mitral valve is damaged most frequently, the aortic next and the tricuspid and pulmonic valves the least. The combination of aortic and mitral valvular disease is not infrequent, while other combinations are rare and difficult to diagnose clinically. It must be remembered at all times in rheumatic heart disease that the myocardium as well as the valves are affected. *It should never be forgotten that the amount of cardiac enlargement is the important factor in prognosis rather than the amount of valvular damage.*

DIAGNOSIS

Usually the quality, location and timing of the heart murmurs in valvular heart disease are not difficult to diagnose with experience. However, it may be necessary to utilize all aids possible in certain instances. Electrocardiographic patterns, fluoroscopy of the individual heart chambers, and timing of the murmurs when there are irregularities of the heart, by concomitant palpation of the carotid artery, will be helpful. Careful consideration of extracardiac factors such as anemia, malnutrition, thyroid dysfunction and bony abnormalities of the thorax are important. Finally it is well known that change in heart rhythm and rate, congestive failure, pregnancy and other factors may change the quality and intensity of the murmurs.

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Mitral Valve Disease.—Rheumatic fever is the main cause of mitral disease. Congenital defects are rare and syphilis does not involve the valve. Atherosclerotic changes occur in elderly patients following rheumatic fever in youth. Relative mitral insufficiency occurs frequently from conditions that strain or dilate and enlarge the left ventricle such as hypertension, aortitis and aortic valve disease. In these conditions a systolic apical murmur is heard owing to dilatation of the mitral muscular ring.

Rheumatic fever produces vegetations along the line of apposition of the valve edges. Later, with recurrent damage, scarring with gradual stenosis and insufficiency may occur. Although stenosis and insufficiency usually accompany each other, the disorders will be described separately.

In *mitral insufficiency* the valve segments do not close properly, producing a systolic apical murmur, either soft or harsh in quality. If intense enough, the murmur may replace the first and second heart sounds. The murmur is high-pitched and often musical. It does not disappear or vary much with respiration or change in position. It must be distinguished from so-called "physiological" or "accidental" murmurs and should be an important guiding sign for a thorough study of the cardiovascular system for other evidence of heart disease.

It is interesting to note that, in the study of men classified as 4F, the specialists making the study concluded "in general, it was agreed that very slight or even slight systolic murmurs at the cardiac apex in the absence of cardiac enlargement or of a clear rheumatic history, especially if they were late in time or dissipated or almost cleared by changes in body position or by forced respiration, should be regarded as unimportant and not disqualifying for military service. Very slight systolic murmurs at the aortic valve area and at the left of the lower sternum were also acceptable in the absence of any evidence of heart disease. Pulmonary systolic murmurs, which are present in many normal persons in the recumbent position, were rarely a cause for rejection per se, only if they were loud and but little affected by respiration were they regarded as evidence of an organic lesion. All diastolic murmurs were cause for rejection, but in occasional cases superficial scratchy to-and-fro sounds, not indicative of cardiac or pericardial disease, were recognized as entirely unimportant." Certainly, individuals with these types of murmurs need not have their physical activities restricted.

On the other hand, *mitral stenosis* can be readily diagnosed, if the characteristic diastolic murmur is present. It is most important to be "mitral stenosis" conscious as the murmur can be easily overlooked. It should be a routine practice to turn the patient on the left side and listen carefully all around the apex area, as the murmur is well local-

ized in most instances. Exercising the patient before this procedure may be necessary to bring out the characteristic murmur. An unusually hard apical thrust is almost diagnostic. The murmur varies greatly as to location in diastole, beginning frequently early in diastole in children, while in adults it may be a sharp, late "crescendo," low pitched, rumbling noise ending in a typical snapping first sound. *This last feature alone can be diagnostic for the trained ear.* In auricular fibrillation, auriculoventricular block and auricular standstill, the loss of auricular tone prevents the crescendo of late diastole and the murmur may be very hard or impossible to elicit. A diastolic murmur appearing during acute rheumatic infection in children does not necessarily mean mitral stenosis and may disappear as the infection subsides.

The electrocardiographic findings of large, notched and broad P waves with right axis deviation, auricular fibrillation and right axis deviation, or large R deflections in CR₁, CR₂ and CR₃ although not diagnostic, are compatible with rheumatic mitral disease. Roentgenographic and fluoroscopic findings of suggestive value consist of "mitralization" of the left heart border, large auricles and right ventricular hypertrophy.

Aortic Valve Disease.—The aortic valve, unlike the mitral valve is affected not only by rheumatic fever but also by syphilis and atherosclerosis. Rheumatic fever causes the same changes as described for the mitral valve. Syphilis primarily attacks the proximal aorta causing its widening, which in turn causes dilatation of the aortic ring and may narrow the orifices of the coronary arteries which start just distal to the valve leaflets. Thus the heart muscle may receive a double burden—the extra load of regurgitation and impaired coronary arterial circulation. In syphilis, the valve leaflets may be involved by the disease also. Hypertension may cause dilatation of the aorta with slight insufficiency. Atherosclerosis of the valve may occur but most pathologists believe that moderate to severe sclerosis, seen mostly in older men, is primarily a scarring of rheumatic origin with later deposits on the affected areas. Although a few cases may be congenital bicuspid aortic valves in adults are thought to be of rheumatic origin.

Aortic Insufficiency.—The murmur of aortic insufficiency is best heard with the patient leaning forward with the breath held in full expiration. Although usually thought to be heard best in the second interspace just to the right of the sternum, it is most often found in the third interspace just to the left of the sternum and often down the left sternal border and even at the apex. It is much higher pitched than the diastolic mitral murmur and often is a short whiff that seems to replace the aortic second sound. It is a tantalizing murmur in that it may appear and disappear inexplicably although all the other signs of free regurgitation may be present such as a "water hammer pulse,"

increased pulsations of visible arteries and widened pulse pressure with lowered diastolic blood pressure readings. It follows that the loudness or duration does not indicate the degree of insufficiency.

It should be pointed out that many of the cases of free aortic regurgitation have an Austin Flint murmur at the mitral area which closely simulates the murmur of mitral stenosis. A differential diagnosis may be very difficult. It is thought that the regurgitation stream hits the mitral leaf setting it in vibration thus producing a diastolic murmur. It should be remembered that the systolic murmur heard with aortic insufficiency is not due to organic stenosis, and that the Graham Steele diastolic murmur of pulmonic insufficiency is so rare that it is of little importance. An aortic diastolic murmur is sometimes heard with hypertension and atherosclerosis but the actual regurgitation is usually slight. The diastolic blood pressure need not necessarily be below normal to make a diagnosis of aortic insufficiency.

Aortic Stenosis.—As stated previously, aortic stenosis is due to rheumatic fever and is rather rare. The usual diagnosis depends on a harsh systolic murmur at the aortic area transmitted to the neck vessels, with a concomitant thrill felt in the same position as for insufficiency, and a small and late pulse. Although it may exist without these signs, it is better to classify it as "suspected," or "probable" in cases with considerable aortic insufficiency.

Tricuspid and Pulmonic Valvular Disease.—These will be mentioned only briefly because of their relative lack of importance from a prognostic standpoint. Pulmonic valvular disease must be distinguished from patent ductus arteriosus. The latter is recognized in the majority of instances by the "machinery" murmur that persists throughout the entire cardiac cycle with accentuation during systole. The murmur is best heard in the second interspace just to the left of the sternal border. An accentuated or split second sound in the pulmonic area is often heard with mitral disease but alone is of no significance. The signs of tricuspid disease are manifested mainly by insufficiency with pulsating liver and peripheral veins. These signs may be due to relative insufficiency during congestive failure and disappear with compensation. The murmurs of tricuspid disease are heard best over the lower sternum but are usually obscured by the concomitant mitral murmurs.

THE MANAGEMENT OF CHRONIC VALVULAR DISEASE

The prevention and the treatment of recurrent rheumatic fever, bacterial endocarditis and allied subjects are comprehensively covered elsewhere in this symposium, as is also the treatment of impending or actual congestive failure. As there is no specific "cure" or treatment of chronically damaged heart valves, we desire to emphasize the person-

ality problem involved, particularly in those patients with slight or no cardiac enlargement and no definite subjective symptoms of circulatory insufficiency

The main objective is to avoid making the patient heart conscious. We frequently encounter patients who, after having been told that they have "a leaking heart valve," developed multiple somatic complaints, none of which existed previously. If a patient must be told that he or she has a valvular defect, it should be done in an optimistic, reassuring manner. It is usually well to tell the patient with *slight or no cardiac enlargement* that the heart muscle is fine and that there is no reason why he or she should not indulge in all common activities, as we have no proof that exercise hastens the natural progression of the pathological picture, while the restriction of physical effort may cause a great deal of unhappiness to the patient and apprehension to the parents. Unless there is definite evidence of moderate to marked decrease in functional capacity and moderate cardiac enlargement, there is no reason why women should not marry and have children, preferably in their early twenties. In other words, these persons should be permitted to lead a normal life. Like the diabetic, they need and should be given reassurance when they are turned down by the military services or life insurance companies, for individually they may outlive their "normal" contemporaries.

In those without actual congestive failure but who give evidence of *limited exercise tolerance and some enlargement*, we know that the myocardium as well as the endocardium is involved. Here again the patient should be permitted all activities that do not cause symptoms. We, as physicians, need only show him how to live within his limitations. He knows best what he can or cannot do. As in other systemic diseases, overweight and overindulgences should be avoided but in the end it is up to the individual to decide how he would lead his life.

Finally, in the case of children and young adults whom we suspect of having valvular heart disease but are not entirely certain, it is far better to tell them that the murmur is "functional" and of no concern than to make a definite diagnosis. It is all too easy to make such a person into a mental invalid more helpless than his valvular lesion would ever make him.

SUMMARY

We have briefly discussed the commoner causes of valvular heart disease, their modes of action and methods for identification of the different valvular heart murmurs. Under management, we emphasized the value of an optimistic viewpoint wherever possible in order to avoid the creation of a "cardiac neurosis."

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DIAGNOSIS AND TREATMENT OF CARDIAC ARRHYTHMIAS

SAMUEL BELLET, M D *

THE subject of cardiac arrhythmias is of considerable importance for several reasons. These disturbances are common. They frequently produce intense anxiety on the part of the patient. The rapid rate often precipitates heart failure. The arrhythmia can in most instances be diagnosed easily either clinically or by graphic methods and results of treatment of these disturbances are among the most satisfactory observed in any field of medicine.

The term "arrhythmia" is frequently used synonymously with clinical disorders of the heart beat and disturbances of the cardiac mechanism. The latter terms are preferable because, while the rhythm is often irregular many of these disorders, for example paroxysmal auricular tachycardia, auricular flutter, complete heart block and others, display an absolutely regular rhythm.

The following information is of help in establishing the clinical diagnosis: the age of the patient, the ventricular rate, the type of heart condition and the presence of irregularities. These disorders are comparatively rare below the age of 10. From 10 to 20 years the types of irregularities encountered are sinus arrhythmia (usually phasic in type), extrasystoles, auricular fibrillation and varying degrees of auriculoventricular heart block.

Between the ages of 20 and 30 most of the irregularities observed are those usually seen in rheumatic hearts: namely varying degrees of auriculoventricular heart block, auricular fibrillation and extrasystoles. From 30 to 45 syphilitic heart disease is also encountered. Although auricular fibrillation is rare in syphilitic heart disease, various degrees of auriculoventricular heart block, extrasystoles and paroxysmal tachycardia are encountered. In addition, the disturbances in the cardiac mechanism following digitalization are observed. From the age of 45 on, one encounters a preponderant number of hearts of the degenerative type.

Other factors of importance in the diagnosis of the arrhythmias are the underlying heart condition, the presence of heart failure, the symptoms and signs presented by the patient, the response to carotid sinus pressure and, finally, the electrocardiographic findings.

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ECTOPIC RHYTHM SHOULD BE SUSPECTED FROM THE FOLLOWING:

- 1 The presence of any irregularity
- 2 A rate below 30 or above 140 per minute with regular rhythm
- 3 History of sudden onset of rapid rate
- 4 Rapid rate coinciding with onset of failure
- 5 Sudden halving of rate with carotid sinus pressure
- 6 Variation in intensity of first heart sound with slow or rapid rate
- 7 No change in rapid rate from moment to moment following exercise
- 8 Electrocardiographic findings

The principles of therapy are not particularly complicated. The number of dependable drugs available is relatively small. However, the doses given and the methods of administration vary in different clinics. The mistake often made is that too little of the drug is given. Frequent clinical rechecks, including the use of graphic methods, will enable one to gauge the optimum dose and will help one to recognize the development of toxic effects in the early stages.

Owing to lack of space, only some of the more common disturbances of the cardiac mechanism will be discussed.

AURICULAR FLUTTER

Auricular flutter is usually seen in patients with moderately advanced or a severe grade of myocardial involvement. It is observed most frequently in association with the degenerative group of heart diseases.

Symptoms and Signs.—The symptoms and signs of auricular flutter are similar to those of other types of accelerated heart action except for the greater tendency to develop heart failure. Since auricular flutter is often observed in the presence of pre-existing myocardial damage in the older age group, and owing to the relatively long duration of the attacks, there is an opportunity for the occurrence of exhaustion of the heart muscle with resulting heart failure.

As a result of the rapid ventricular rate, a pulsus deficit is often observed. In many cases there is an associated pulsus alternans. With slow ventricular rates (40 to 60 per minute) one may occasionally be able to hear the individual auricular beats. These have been recorded graphically. With 1-to-1 flutter the ventricular rate ranges from 220 to 280 per minute, the heart muscle becomes rapidly exhausted and these patients present the picture of shock, with a severe grade of both right and left heart failure.

Emboic phenomena are observed in about 7 per cent of these patients.

Diagnosis—The diagnosis of auricular flutter is to be considered in any patient presenting evidence of an ectopic rhythm with a regular apical rate ranging from 140 to 180 per minute. It must be differentiated from all varieties of paroxysmal tachycardia, from rapid simple tachycardia and, when the ventricular response is irregular, from auricular fibrillation. With 3 to-1 and higher grades of auriculoventricular heart block, it is difficult to diagnose auricular flutter except by graphic methods.

Carotid sinus pressure in auricular flutter results either in no ventricular slowing or in ventricular slowing which is maintained only

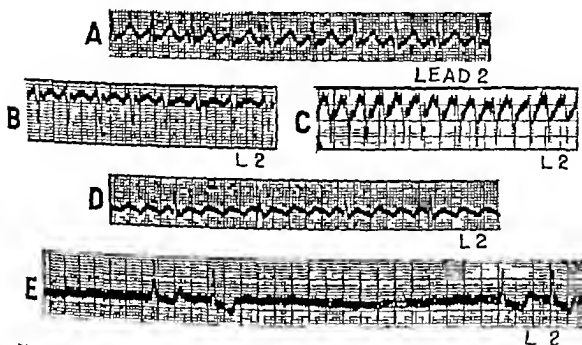


Fig. 151.—*Auricular Flutter* A, Shows a flutter with 2-to-1 auriculoventricular heart block. The ventricular rate is 120 per minute and the auricular rate is 240 per minute. B, Also shows 2-to-1 auriculoventricular heart block. C This strip is from the same case and shows a period of 1 to-1 flutter with the ventricles responding to every auricular impulse at a rate of 260 per minute. D Shows the ventricles responding to every fourth beat of the auricles E, Shows auricular flutter with high grade auriculoventricular heart block which was caused by the action of digitalis.

during the period of carotid sinus pressure, the rate returning immediately to its original speed when the pressure is removed. The effect of carotid sinus pressure in auricular flutter is enhanced by digitalis, prostigmine and other vagal stimulants, so that where carotid sinus pressure alone was previously ineffectual it may become effectual after the administration of these drugs.

The diagnosis of auricular flutter is usually clearly established by the electrocardiogram. Although any lead may be used, auricular waves are most clearly delineated in the CR₁ position of the precordial leads and are best seen directly after carotid sinus pressure, as a result

of which auricular cycles are seen unobscured by the ventricular complexes

Treatment—Digitalis is the drug of choice in the treatment of auricular flutter. In addition to being a cardiac stimulant, digitalis will break up the auricular flutter in about 70 per cent of the cases. In most instances, the flutter is converted to an auricular fibrillation*. Digitalis is then stopped, after which fibrillation reverts to normal rhythm spontaneously in about two-thirds of the patients. If fibrillation tends to persist after a period of one to two weeks, quinidine may be tried in an endeavor to convert the auricular fibrillation to a normal rhythm. The use of quinidine to restore normal rhythm is indicated in those cases of auricular fibrillation in which the onset of the irregularity is of recent origin, the heart is not severely diseased, and the enlargement of the left auricle is not considerable in degree. In such instances, quinidine is successful in converting auricular fibrillation to a normal rhythm in over one-half of the hearts. Occasionally quinidine converts auricular fibrillation back to auricular flutter.

Quinidine sulfate is the drug of second choice in the treatment of auricular flutter and, for all practical purposes, its use should be restricted to those cases in which digitalis has failed to break up the flutter. Quinidine is successful in converting auricular flutter to a normal sinus rhythm in about 20 to 30 per cent of cases. This drug is a protoplasmic poison and should be used with caution, especially where large doses are required and in the presence of severe myocardial damage. In the presence of congestive heart failure it should rarely be used. Quinidine, when successful, converts the flutter directly to normal sinus rhythm without an intermediate period of auricular fibrillation.

The auricular rate under quinidine may drop as low as 135 per minute. The ventricular response also changes, due to vagal paralysis; the degree of auriculoventricular heart block changes from 2-to-1 to 1-to-1, so that with an auricular rate of 135 per minute the ventricular rate may also be 135 per minute.

The use of beta-methylcholine has also been suggested for the purpose of breaking up auricular flutter. However, this drug causes a profound fall in the blood pressure and its use for the treatment of auricular flutter is not recommended.

Where auricular flutter is associated with rapid ventricular rates and a severe grade of heart failure, and where absorption of the drug may be slow or uncertain, one may resort to the use of a preparation intravenously or intramuscularly, which is somewhat safer. For the intravenous route, strophanthin $\frac{1}{100}$ grain may be used, for the intramuscular route, 3 to 5 cat units of digalen may be administered.

*Occasionally, flutter is converted into normal rhythm by digitalis without a recognizable period of auricular fibrillation.

We have observed two patients in whom carotid sinus pressure following digitalization converted auricular flutter to auricular fibrillation. This transition was recorded electrocardiographically

AURICULAR FIBRILLATION

Auricular fibrillation is almost always observed in the presence of myocardial disease, which is frequently of an advanced grade. It is rarely observed in normal hearts. The arrhythmia is observed in 60 per cent of the patients with heart failure. The most frequently associated factor is hypertensive, arteriosclerotic cardiovascular disease and the next most frequent is rheumatic heart disease, these two conditions accounting for about 90 per cent of the cases of auricular fibrillation. Other associated factors are thyrotoxicosis and toxic states. It is rarely observed in syphilitic heart disease except in association with hypertension and arteriosclerosis. In the earlier decades rheumatism is the most frequent etiologic factor, in the later decades (sixth and seventh), during which the incidence is highest, degenerative lesions predominate. Auricular fibrillation is rare below the age of 15, it is more common in men than in women but the preponderance of males is chiefly in the nonrheumatic group; in the rheumatic group the incidence is about equal.

Symptoms and Signs.—Patients with auricular fibrillation almost invariably demonstrate evidence of myocardial abnormality, often of severe grade. They usually manifest evidence of heart failure: breathlessness, fatigue on slight exertion, precordial oppression, cyanosis, cardiac enlargement, rales at the lung bases, pleural effusion, edema of the legs and ascites.

Auscultation reveals a characteristic type of irregularity. This is most pronounced clinically at rates ranging from 90 to 130 per minute. When the ventricular rate is slow or very rapid, the typical irregularity is difficult to determine clinically. It is also difficult to distinguish clinically from auricular fibrillation and multiple extrasystoles arising from different foci. The irregularity due to auricular fibrillation becomes more marked after exercise. Extrasystoles are usually abolished by exercise resulting in a regular rhythm.

At fairly rapid rates during a short cardiac cycle, the ventricular contraction often fails to raise the aortic valve. As a result, one heart sound only is heard, and the ventricular contraction is too weak to produce a pulse at the wrist. When many such contractions occur a marked variation, or pulsus deficit arises between the apical and pulse rates.

The heart sounds vary considerably in intensity. The loudest sounds are heard following the longer pauses which permit greater ventricular filling, the faintest sounds occur following the short cycles. Cardiac

murmurs undergo significant changes with the onset of auricular fibrillation. Systolic murmurs which were audible during normal rhythm are preserved during fibrillation. They vary considerably in intensity, depending upon the length of the preceding cycle, they are louder after the longer cycles and fainter after the shorter cycles, as a result of changes in ventricular filling. With rapid rates the murmurs often become inaudible. The presystolic murmur of mitral stenosis, due to failure of the auricles to contract, is replaced by a diastolic rumble with the onset of auricular fibrillation. Its intensity and the portion of the diastole in which it is heard vary with the cycle length.

Diagnosis.—The diagnosis of auricular fibrillation may be suspected clinically in a patient manifesting an atypical type of irregularity who presents evidence of advanced myocardial disease of the types men-

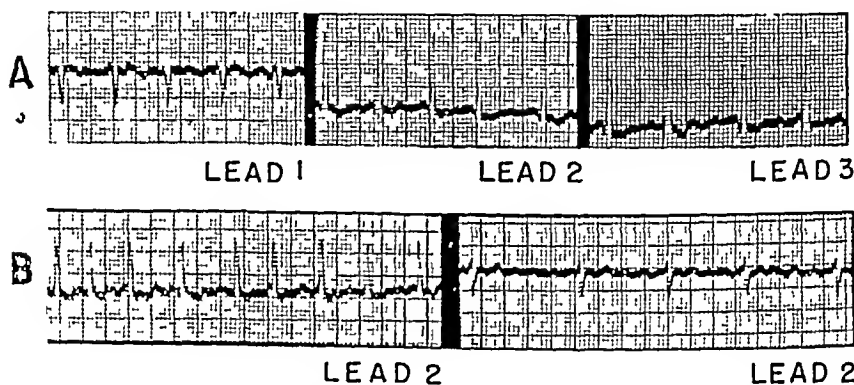


Fig 152—Auricular Fibrillation A, Shows the three limb leads in a patient with advanced mitral stenosis and auricular fibrillation B, The first strip shows auricular fibrillation with a moderately rapid rate which averages 125 per minute. The second strip shows auricular fibrillation with a slower ventricular rate averaging 64 per minute.

tioned previously, and especially if the patient is observed in congestive failure. The characteristic symptoms and signs have already been discussed. Clinically, auricular fibrillation must be differentiated from multiple extrasystoles arising from different foci and auricular flutter associated with varying degrees of heart block. In these two conditions, exercise tends to make the rhythm quite regular, whereas in auricular fibrillation the rhythm becomes more irregular. The electrocardiogram usually establishes the diagnosis beyond doubt.

Treatment.—Since auricular fibrillation is usually associated with varying degrees of heart failure, therapy should be directed to this state in addition to the treatment of the irregularity. Digitalis is the drug of choice in the treatment of auricular fibrillation. Digitalis acts by impeding the passage of impulses from auricle to ventricle and

thus slows the ventricular rate. This is accomplished by a direct muscular and by a vagal effect on the auriculoventricular node. The maximum therapeutic effect is said to be reached when the apical rate drops to about 70 per minute with an elimination of the pulsus deficit. Digitalization may be performed rapidly in patients with a severe grade of heart failure and rapid rates or slowly in those patients in whom failure is of slight or moderate degree.

The approximate dose required for a 150 pound person is about 22 grains of the powdered leaf. This may be given over a period of four to five days when slow digitalization is adequate or within about two days when rapid digitalization is necessary. When the patient presents a picture of severe congestive failure which necessitates rapid digitalization and definite absorption, the parenteral route is indicated. Strophanthin $\frac{1}{100}$ grain may be given intravenously followed in two to three hours by $\frac{1}{200}$ grain. This last dose may be repeated if necessary in about five hours. Digalen, 2 to 3 cat units, may be administered intramuscularly and repeated one or two times in six to eight hours, depending upon the effect on the heart of previous doses. Digitalis is contraindicated in patients with a slow ventricular rate that is below 50 per minute (independent of treatment) and should not be given where the ventricular rate following therapy has decreased to 40 or 50 beats per minute. In such cases further slowing of the ventricular rate does harm by increasing the diastolic volume, which leads to stretching of the already diseased cardiac fibers. The dosage of digitalis required to produce the desired therapeutic effect varies considerably, depending upon the age of the patient and the underlying pathologic state.

In the presence of thyrotoxicosis or other toxic states, and in patients with increased sympathetic tone, the dosage required to maintain a ventricular rate of 70 to 80 per minute is usually higher than the average. On the other hand, in older patients with sclerotic changes in the auriculoventricular node and those with overactive vagal tone, smaller doses usually suffice to slow the ventricular rate. Patients with aortic stenosis are particularly sensitive to digitalis and usually can tolerate only small doses. It should be emphasized that the reduction of the apical rate to 60 or 70 does not necessarily coincide with the maximum degree of improvement in so far as signs of congestive failure are concerned. Frequently edema may be present even at these slow rates. In such instances digitalis should not be increased. Instead, the signs of failure should be treated by diuretics and other procedures.

Toxic effects of digitalis manifest themselves by the appearance of numerous ventricular extrasystoles, coupled rhythm and sequences of two or more ectopic ventricular beats. With continuance of the drug, paroxysmal ventricular tachycardia may result. This is a dangerous

type of arrhythmia since it predisposes to ventricular fibrillation, which is usually incompatible with life. It should be emphasized that these toxic effects may occur in the absence of nausea, vomiting and other frequently mentioned toxic manifestations. These ectopic rhythms may be avoided by carefully supervising the digitalis dosage and carefully following the progress of the patient clinically and electrocardiographically. When such toxic effects appear, digitalis should be stopped immediately. Should the effects continue to the stage of ventricular tachycardia, quinidine sulfate may be administered in an effort to abolish this arrhythmia (see p. 1323).

The continuance of auricular fibrillation involves three dangers: the circulatory dynamics are relatively inefficient as compared with those present with normal rhythm, continuous digitalization is required, and, most important, there is a constant danger of embolic phenomena leading to serious complications.

Quinidine sulfate is indicated in the treatment of auricular fibrillation where it is desired to convert the irregularity to a normal sinus rhythm. It is indicated where the onset of fibrillation is relatively recent, where the heart is not severely diseased, and where the auricles as observed fluoroscopically are not greatly enlarged. In such cases, quinidine is efficient in converting the fibrillation to normal rhythm in over 50 per cent of patients. Frequently quinidine administration must be maintained for two to three months after restoration of normal rhythm since cessation of its administration may lead to the return of auricular fibrillation. Quinidine sulfate is also indicated in the prevention of attacks of paroxysmal auricular fibrillation, when such attacks occur frequently.

One of the dangers to be considered in the restoration of normal rhythm by the use of quinidine is the possibility of emboli being thrown off into the circulation. Statistics relative to this occurrence vary considerably because it is difficult to differentiate embolic phenomena which occur as a result of the underlying cardiac state. In those cases in which the fibrillation is of less than three months' duration, the danger of embolic phenomena is slight, compared with the benefits to be derived.

Auricular fibrillation which results from thyrotoxicosis usually disappears with restoration of a normal basal metabolism following successful thyroid surgery. Quinidine may be of help in those patients in whom the restoration of normal rhythm is somewhat delayed.

Auricular fibrillation which results from active rheumatic infection, toxic processes or a disturbance of metabolism tends to return to normal rhythm with the cessation of these processes unless the auricular muscle has been severely damaged, with resultant irreversible changes.

PAROXYSMAL AURICULAR TACHYCARDIA

Two types of paroxysmal auricular tachycardia may be observed. In the common type the ventricles respond to every beat of the auricles, in the less common type the auricular tachycardia is associated with varying degrees of auriculoventricular heart block, so that with an auricular rate ranging from 150 to 200 per minute there is a resulting ventricular rate of 75 to 100 per minute. Patients subject to attacks of paroxysmal auricular tachycardia sometimes present electrocardiograms which during the period of normal rhythm show a short P R interval with a widened QRS complex (Wolff Parkinson White syndrome). Aside from the tendency of these patients to develop this arrhythmia, their hearts may be normal.

The underlying etiology in paroxysmal auricular tachycardia is not known. Since this disturbance is observed in a considerable number

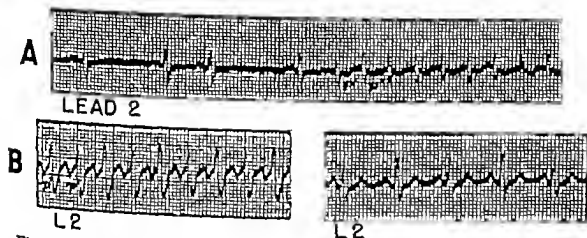


Fig 153—*Paroxysmal Auricular Tachycardia* A, Shows normal rhythm with the onset of a paroxysm of auricular tachycardia during which the auricles and ventricles beat at a rate of 200 per minute. B The first strip shows an auricular tachycardia with a rate of 200 per minute. Note widening and notching of the ventricular complexes with the rapid rate. The second strip is from the same case after restoration of normal sinus rhythm.

of hearts (about 50 per cent) which are considered clinically normal various theories for its production have been advanced. Among them are disturbances of the physiochemical mechanism in the auricles allergic states and high degrees of sympathetic tone. In the remaining 50 per cent, this condition is observed in the presence of damage to the auricular muscle in patients with rheumatic, hypertensive or arteriosclerotic heart disease and with toxic states. The type of auricular tachycardia associated with auriculoventricular heart block is observed usually in the older age groups, in association with toxic digitalis effects, and in the presence of coronary arteriosclerosis.

Symptoms and Signs—The symptoms of paroxysmal auricular tachycardia are similar to those observed in the presence of any ectopic rhythm and depend largely upon the state of the heart muscle and its

response to an acceleration of the heart beat, the duration of the paroxysm and the nervous make-up of the patient. These may vary from a relative freedom from symptoms, except for slight palpitation, to varying degrees of precordial discomfort and a feeling of marked anxiety associated with considerable precordial pain.

The signs of paroxysmal auricular tachycardia are those of an accelerated heart action superimposed on the types of hearts mentioned previously. Gallop rhythm and pulsus alternans are encountered not infrequently during the paroxysm. Heart failure and the anginal syndrome may also be observed. Occasionally, especially in the older age group with arteriosclerosis, the paroxysm may precipitate the picture of shock resembling that of an acute myocardial infarction. Death occurring during paroxysmal auricular tachycardia is rare, but has been observed.

Diagnosis.—The diagnosis of paroxysmal auricular tachycardia should be suspected in a patient who gives a history of sudden acceleration of the heart beat which lasts for varying periods of time and stops suddenly. The previous presence of auricular extrasystoles is suggestive evidence. The presence of a regular rhythm during the paroxysm, the rate of which ranges from 140 to 220 per minute, should lead one to suspect paroxysmal auricular tachycardia as the cause. The differential diagnosis involves simple tachycardia, auricular flutter and ventricular tachycardia. Of these three abnormal mechanisms, paroxysmal auricular tachycardia is the only one which, when responding to carotid sinus pressure, results in a sudden halving of the rate. With restoration of the normal mechanism, the latter being maintained for relatively long periods of time. Ventricular tachycardia is uninfluenced by carotid sinus pressure, as previously stated, auricular flutter, when it responds, presents a slowing of the ventricular rate which is maintained only during the period of carotid sinus pressure.* The final diagnosis is usually clearly established by the electrocardiogram.

Treatment—The treatment of simple paroxysmal tachycardia may be divided into (A) treatment during attacks, (B) treatment between attacks.

A. During the attacks the following procedure may be tried: application of carotid sinus pressure. In order to apply this pressure properly, the patient should be placed in the recumbent or semirecumbent position. The carotid artery should be palpated as high up in the neck as possible and pressed firmly against the vertebral column. This vessel is frequently an elusive structure and one must make certain that the carotid artery and not soft tissue of the neck is pressed upon. During

* Occasionally patients with sinus tachycardia, with a sensitive carotid sinus mechanism, the sensitivity possibly enhanced by digitalis, respond similarly by a sudden decrease in the ventricular rate. Usually the rate returns to the previous figure upon removal of carotid sinus pressure.

the maintenance of pressure a stethoscope should be applied to the precordium, and as soon as the heart stops the pressure should be removed.* Bilateral carotid sinus pressure should never be applied simultaneously. We have never seen any accidents result from the procedure when applied as directed. The patient himself as a result of experience, frequently employs similar procedures, such as pressure applied to various parts of the neck, particularly in the region of the carotid sinus, bending down, stretching the neck as far back as possible, holding the breath, or inserting the finger in the throat to induce vomiting. The rationale of all these procedures is vagal stimulation.

The following drugs may be given during the paroxysm if carotid sinus pressure fails to restore normal rhythm.

1. Digitalis intramuscularly, 2 to 3 cat units repeated in one to two hours if necessary. Intravenous administration has also been recommended, but we rarely find this necessary. Carotid sinus pressure, if previously ineffective, slows the heart beat after digitalis administration.

2. Magnesium sulfate, 10 cc. of a 20 per cent solution administered intravenously.

3. Calcium gluconate, 10 cc. of a 10 per cent solution administered intravenously. If the drug is efficacious, the paroxysm will cease immediately.

4. Quinidine sulfate, 5 grains administered intramuscularly at hourly intervals for 5 or 6 doses or more. Quinine dihydrochloride 5 grains dissolved in 20 to 50 cc. of normal saline solution, may be given slowly by vein or an ampule of 5 cc. may be given subcutaneously. Quinidine may be given by mouth 3 to 5 grains every hour for 10 or more doses.

5. Mecholyl, 25 to 50 mg. subcutaneously. This often results in cessation of the paroxysm, however, this drug usually produces a profound fall in the systemic blood pressure. We have observed periods of ventricular fibrillation after its administration and advise caution in its use in the very young or the very old, and in asthmatic individuals. When the drug is given, one should always have a syringe of $\frac{1}{30}$ grain of atropine ready for administration in the event of untoward effects.

6. Ipecac given by mouth in syrup form in a dose of 1 to 4 drams to induce vomiting.

7. Prostigmine methylsulfate, 1 to 2 cc. of 1:2000 solution, given intramuscularly. While it may not be effective in itself it increases the sensitivity of the carotid sinus about twenty minutes after its administration, so that the previously insensitive carotid sinus is frequently rendered sensitive to stimulation.

* Recently Askey (Am. Heart J., February 1946) collected ten cases in which carotid sinus pressure resulted in either transient or permanent hemiplegia. With the technic described, we have never observed such a complication in many thousands of cases.

B The treatment between attacks involves ascertaining the precipitating cause of the attacks, if possible, and treating it. Nervous states, abdominal distention, excessive exertion and allergic factors all may be provocative causes. If the paroxysms occur frequently, the following procedures are usually helpful: quinine sulfate, 3 grains given four to five times per day, digitalization, followed by a maintenance dose which may be continued for months. Occasional cases are encountered in which these procedures do not suffice and the paroxysms continue.

AURICULOVENTRICULAR HEART BLOCK

Auriculoventricular heart block may be divided into two types: partial and complete. The first stage of auriculoventricular heart block is said to occur when the auriculoventricular conduction (P-R interval) exceeds 0.20 second. As the degree of block increases the conduction time becomes longer and longer until dropped beats occur, that is, the ventricles fail to respond to some auricular beats. As this condition progresses, the degree of block may increase to 2-to-1, 3-to-1, 4-to-1 or still higher degrees of auriculoventricular heart block. As the block further increases, a stage is reached at which the ventricles fail to respond to any auricular impulses, with the result that these two chambers beat entirely independently of each other. When this stage is reached, the auriculoventricular heart block is said to be complete.

Symptoms and Signs—In partial auriculoventricular heart block, no symptoms are observed as being due to the block itself, even with a slow ventricular rate, the symptoms are those of the underlying disease. In the usual case of complete auriculoventricular heart block, the only symptoms observed are fatigue on exertion, consciousness of the slow beating of the heart and occasional precordial pain. These patients usually cannot engage in strenuous physical exertion but generally do fairly well on a regimen of reduced activity.

As a result of the slow rate, alterations appear in the cardiovascular dynamics. The cardiac output per beat is increased but the cardiac output per minute is decreased. The systolic blood pressure rises to about 170 to 200 mm. and left ventricular hypertrophy results. These patients are subject to Stokes-Adams attacks, which are discussed later.

Diagnosis—When prolongation of the conduction time (prolonged P-R interval) is present, a diminished intensity in the first heart sound results, which may be marked. If the P-R interval is sufficiently prolonged, it may produce a gallop sound (summation gallop). This is best heard at rates over 100 per minute and is the result of auricular contraction superimposed upon the wave of early diastolic ventricular filling. With higher grades of partial block, dropped beats may be detected. These pauses may be abolished by exercise, they are at times difficult to differentiate from the compensatory pause following an

extrasystole Occasionally the auricular sounds may be audible in the higher grades of auriculoventricular heart block.

When the heart beats regularly between 30 to 50 per minute, an auriculoventricular heart block may be suspected In partial block, exercise or amyl nitrite may abruptly double the ventricular rate. When the apical rate is regular, ranges from 20 to 40 per minute and is unaffected by exercise or atropine, complete auriculoventricular block should be suspected. The first heart sound varies in intensity because of the varying auriculoventricular intervals When the auricular and ventricular contractions occur close together, the first sound is relatively loud, when they are far apart, the first sound is faint.

The important symptoms to be considered in the higher grades of partial and complete block are the development of giddiness fainting and temporary loss of consciousness (Stokes Adams syndrome) These seizures occur during the transition from partial to complete block, as

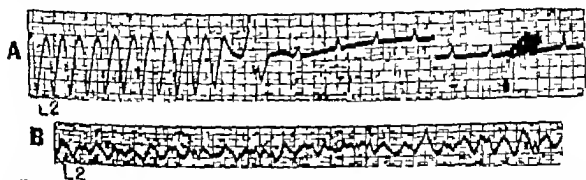


Fig 154—Tracing Taken During Stokes Adams Seizure A, Shows a prefibrillary type of ventricular tachycardia followed by a period of ventricular standstill The cycles occurring regularly at a rate of 88 per minute represent auricular beats B An example of ventricular fibrillation

well as during the course of complete auriculoventricular heart block They result from the periods of asystole, which last from three to nine seconds or longer, and consist of syncopal attacks or actual convulsive seizures The following are the underlying mechanisms recorded electrocardiographically during the seizures (a) a prefibrillary type of ventricular tachycardia (b) ventricular fibrillation (c) standstill of the whole heart, (d) ventricular standstill with maintenance of auricular beating. These mechanisms may occur singly or in combination Recognition of these various types is important in therapy Death frequently occurs during a paroxysm indeed this is the most frequent cause of death in complete auriculoventricular heart block. The patient may experience many seizures before death finally supervenes some times over a period of several years

Treatment.—No treatment is required for minor grades of auriculoventricular heart block. The treatment is that of the underlying cause if ascertained for example rheumatic heart disease or other infection Although digitalis may be administered to patients with auriculoven-

tricular heart block, one should be somewhat more cautious in its administration because of their greater susceptibility to higher grades of auriculoventricular heart block

The higher grades of auriculoventricular heart block are usually chronic and fixed. The routine of the patient should be governed by his general fitness. All those who experience syncopal attacks should be warned of the danger of going about alone. We have seen such patients who have been treated for years for epilepsy. Ephedrine sulfate, $\frac{3}{8}$ grain, or similar drugs may be given to prevent such attacks.

The treatment of attacks of Stokes-Adams syndrome depends upon the underlying mechanism, which unfortunately cannot be determined during the attacks except by graphic means. The following measures may be used during the attacks: direct, vigorous thumping on the precordium (more likely to help ventricular standstill), intracardiac injection of adrenalin (for the same type). The occurrence of frequent seizures, one following another, is usually associated with a severe degree of cerebral anoxia and usually signifies a terminal event. We have seen this state improve after use of oxygen and the intravenous injection of aminophylline. To prevent the paroxysms, ephedrine sulfate, $\frac{3}{8}$ grain three times daily, or other sympathicomimetic drugs may be given. Thyroid extract and barium chloride have also been used. Where these attacks are associated with the prefibrillary type of ventricular tachycardia or ventricular fibrillation, quinidine may be given prophylactically.

EXTRASYSTOLES

Symptoms and Signs.—There may be no symptoms in the presence of extrasystoles. Frequently the patient is conscious of what he calls "palpitation" or "the heart turns over" or "the heart stops." Although extrasystoles per se may be of little or no importance, the thought that there is something wrong with the heart renders the patient panicky and he feels the imminence of a serious eventuality. Occurring frequently, these symptoms may arouse intense anxiety on the part of the patient. The history frequently given is that the symptoms are more apparent while resting, particularly while lying in bed.

Diagnosis.—The interruption of a normal rhythm by premature beats followed by a pause which usually, but not invariably, is compensatory is a characteristic finding on auscultation. These pauses are often difficult to differentiate from those that appear during the Wenckebach phenomenon of partial auriculoventricular heart block. When the period between the extrasystoles and the preceding normal beat is short, ventricular filling is small and the extrasystolic beat may not be sufficiently strong to open the aortic valve and will not produce a palpable pulse at the wrist. This results in a pulsus deficit.

The presence of a normal beat followed by an extrasystole repeated in regular sequence is characteristic of coupling. Clinically, the coup-

ling may be mistaken for pulsus alternans because of the alternation of weak and strong beats. The difference here lies in the rhythmic irregularity due to the compensatory pauses following the extrasystoles. In pulsus alternans the rhythm is quite regular. When extrasystoles occur frequently and arise from many different foci, the rhythm is indistinguishable from that of auricular fibrillation. Most extrasystoles disappear following exercise but occasionally they become more frequent with exercise. The latter type is the more serious variety and is the result of myocardial damage. The diagnosis of extrasystoles and their exact origin may be determined by electrocardiography.

Treatment—The treatment of extrasystoles is frequently rather unsatisfactory. Therapy should be directed to the underlying cause if it can be determined. If some type of cardiac disease is present, improvement of the heart by rest, diuretics and digitalis may abolish the extrasystoles. Gastrointestinal disturbances, foci of infection and exogenous poisons should be sought for and removed, if possible. Frequently the cause cannot be found, and patients with the symptomatic variety of extrasystoles should be reassured that this is a normal phenomenon occurring frequently in normal hearts. If they prove troublesome to the patient, the following therapy is suggested: quinidine sulfate 3 grains four or five times daily; papaverine, 1 to 3 grains three times daily, potassium acetate, 2 to 4 gm. in a 25 per cent solution of peppermint water every four to six hours, bromides 15 grains three times daily, phenobarbital, $\frac{1}{2}$ grain three times daily. Psychotherapy is indicated in those cases in which emotional problems may be a factor in the production of the extrasystoles.

PAROXYSMAL VENTRICULAR TACHYCARDIA

Paroxysmal ventricular tachycardia is a rather rare, but serious, type of arrhythmia. When a series of six or more ventricular extrasystoles occurs in succession they may be said to constitute a paroxysm of ventricular tachycardia. Its evolution may be observed in serial tracings. Occasional ventricular extrasystoles initially present are observed to become more numerous and later either coupled rhythm appears or these extrasystoles are observed to occur in sequences of two or three beats. Following this short and then long paroxysms of ventricular tachycardia may appear. A paroxysm may last a few hours, days or weeks. The danger of this disturbance lies not only in its association with a severely damaged heart and the tendency to exhaustion of the heart muscle but also in the predisposal of the rhythm to develop into ventricular fibrillation.

Paroxysmal ventricular tachycardia almost always occurs in the presence of severe myocardial damage. It is only occasionally observed in patients whose hearts are apparently normal clinically. The following

are the most important associations toxic digitalis effects, myocardial infarction, severe grade of hypertension and arteriosclerotic heart disease

Symptoms and Signs.—The symptoms of paroxysmal ventricular tachycardia are similar to those of any ectopic rhythm but are apt to be more severe since they are observed in seriously damaged hearts

Diagnosis—The diagnosis of ventricular tachycardia is difficult to establish clinically, it can be made definitely only by the electrocardiogram. It should be suspected whenever the ventricular rate varies from 130 to 180 per minute and does not yield to carotid sinus pressure. Strong and Levine¹ have mentioned two factors of importance (1) slight irregularity of the ventricular rate and (2) variation of in-

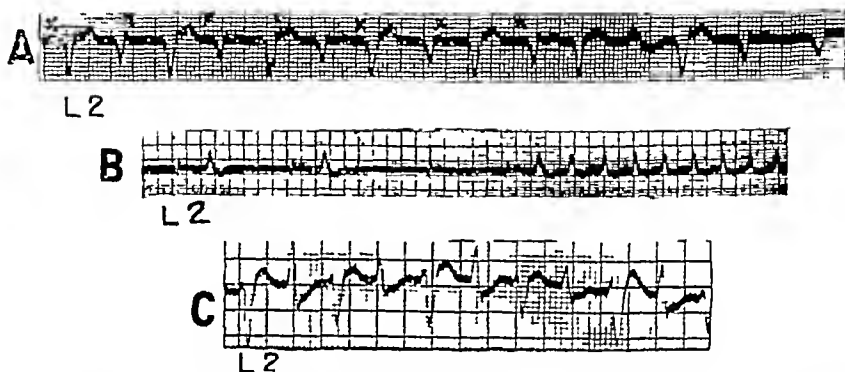


Fig 155—*Paroxysmal Ventricular Tachycardia* A, This strip shows widening and notching of the ventricular complexes of the type which resembles ventricular extrasystoles. Note that the P waves occur independently of and slower than the ventricular complexes. B, Shows auricular fibrillation with coupled ventricular extrasystoles and the beginning of a paroxysm of ventricular tachycardia. C, This strip is an example of the bidirectional type of ventricular tachycardia. This was the result of the toxic action of digitalis.

tensity of the heart sounds because of the superimposition of auricular and ventricular contractions at various beats. The electrocardiographic diagnosis of ventricular tachycardia may be established from the following: the beats of the paroxysms must be ectopic in origin and must conform to those observed as isolated extrasystoles before the onset of the paroxysms, the first beat of the paroxysm must bear the same relation to the preceding normal beat as a coupled extrasystole bears to the preceding normal beat, the ventricles must be observed to beat regularly at a rate of 130 to 180 per minute, and the auricles must also beat regularly, slower than and entirely independent of the ventricles. Occasionally ventricular tachycardia is observed in the presence of auricular fibrillation.

The differential diagnosis from the electrocardiographic standpoint involves an ectopic rhythm in which the QRS complexes are widened

as a result of fatigue of one of the bundle branches incident to the rapid rate. Such widening of the QRS complexes may be observed in auricular tachycardia, auricular flutter and nodal tachycardia

Treatment—The drug of choice in the treatment of paroxysmal ventricular tachycardia is quinidine sulfate. This may be given orally, intravenously or intramuscularly. The dose given orally or intramuscularly ranges from 3 to 5 grains four to five times per day. Sometimes larger doses, up to 10 grains per hour, are given for 10 or more doses. The intramuscular route is used when the patient is in some degree of shock and absorption by mouth may be slow and uncertain. Occasionally quinine dihydrochloride, 5 grains diluted in 20 to 50 cc. of normal saline solution, is effective when given intravenously. Quinidine acts in stopping a paroxysm of ventricular tachycardia by increasing the refractory period of the ventricle. Other drugs which have been used are potassium chloride 2 gm. every two to four hours to supplement or reinforce the action of the quinidine; atropine sulfate, $\frac{1}{2}$ to 1 grain hypodermically; magnesium sulfate 15 cc. of a 20 per cent solution; papaverine, 3 to 5 grains every three hours. The treatment by quinidine is effective in about one-half to two-thirds of the cases. The mistake often made is that the patient is not given enough of this drug.

Prognosis.—The prognosis of paroxysmal ventricular tachycardia is extremely serious because it occurs in hearts which already are severely damaged and its duration for a prolonged period of time predisposes to ventricular fibrillation which as mentioned is usually incompatible with life.

TREATMENT OF RAPID ECTOPIC RHYTHMS WHEN EXACT DIAGNOSIS BY ELECTROCARDIOGRAM IS NOT AVAILABLE

Not infrequently one encounters patients with rapid heart rates which are the result of an ectopic rhythm. These patients are often in a severe state of heart failure and, in the absence of an electrocardiogram, the question often arises as to the proper treatment. The following summarizes the principles of therapy in those cases:

1. Over 90 per cent of ectopic rhythms with rates ranging from 140 to 180 per minute are due to rapid auricular fibrillation, auricular tachycardia and auricular flutter.
2. These arrhythmias usually respond to digitalis action, and its administration may be life saving.
3. Digitalis is of no value in ventricular tachycardia; it is of course contraindicated when this tachycardia is the result of toxic digitalis effects.

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THE DIAGNOSIS AND TREATMENT OF THE COMMON PERIPHERAL VASCULAR DISEASES

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Not infrequently the doctor has viewed his patient with peripheral vascular occlusive disease with a feeling of futility. The diagnosis is commonly described as "poor circulation" and the treatment, as is customary in a disorder wherein we are ignorant of the cause, is casual and vague. For those who are especially interested in this group of diseases, however, as it is with those who take a special interest in any phase of medicine and surgery, the effort to make an accurate diagnosis and to prescribe worthwhile treatment is interesting and quite satisfying. The mind is stimulated by the new theories advanced from every quarter on etiology, pathogenesis and modes of treatment.

In this clinic the most common peripheral vascular diseases are arteriosclerotic, arterio-occlusive diseases with and without diabetes, thromboangitis obliterans, Raynaud's disease, and venous thrombosis (Varicose veins do not come within the scope of this paper.)

PERIPHERAL ARTERIOSCLEROSIS

Peripheral arteriosclerosis is a disease of increasing incidence over the age of fifty, more frequent in men than women. It rarely involves the upper extremities and is more likely to be unilateral as compared with other peripheral vascular diseases. The association of diabetes is frequent and tends to lower the age incidence of this disease.

These patients eventually complain of coldness or paresthesias of the lower extremities. Intermittent claudication or indolent ulcers of the involved extremity may bring them to the doctor. On examination the affected extremity is cold and blanches completely on elevation. Arterial pulsations in the involved foot are absent. The sclerotic process may be so extensive as to produce obliteration of popliteal and femoral pulses. Additional studies include x-ray examination, which usually shows marked calcification of the major vessels. The vasodilator response is diminished. There may or may not be associated vasospasm.

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ered. This should always be of a preganglionic type. Another adequate means of filling the capillary bed may be found in obstructing the venous return by ligating and dividing the superficial or common femoral veins.

Where gangrene has progressed to the point that a serviceable limb may not be salvaged, or where infection further complicates the picture, amputation must be considered. The extent of the gangrenous process may be evaluated by the use of fluorescein and inspection of the tissues under a Woods' filter. If the process is confined solely to a digit, amputation with a racket-shaped incision and excision of the metatarsal head is desirable. Therapeutic refrigeration is very satisfactory but refrigeration is seldom used as an anesthetic agent. Primary closure is seldom possible. The open lesion may be benefited by daily treatments with activated zinc peroxide. In this clinic it has been the practice to confine major limb amputation to the supracondylar region. This provides a fairly useful stump for prosthesis and there is minimal trauma to tissues during the procedure.

THROMBOANGITIS OBLITERANS

The etiology of this inflammatory obliterative vascular disease is unknown, but we consider the relationship of epidermatophytosis and tobacco sufficiently important that we treat the skin of the feet of all patients with some mild fungicide and absolutely prohibit smoking wherever possible.

The Jewish race seems especially susceptible to this disease, which seems to be particularly a disease of men. Many of us have never seen a case among women. However, in young women of the child-bearing age in whom thromboangitis obliterans is suspected or evident, a sensitivity to ergot and its derivatives must be watched for. Ergot poisoning in this susceptible patient may be fatal. Unlike arteriosclerosis, thromboangitis obliterans occurs predominantly among the younger age groups and has its highest incidence under the age of 45.

Usually patients are admitted complaining of cold extremities and intermittent claudication. There may be a history of migratory phlebitis. Not uncommonly they complain of a painful lesion which has developed incident to some rather innocent trauma. These lesions often produce "rest pain" which is quite severe and requires continuous sedation. Examination reveals reduced or absent pulsations and blanching on elevation. A return of color that is abnormal, best described as rubor, with some evanescence, is diagnostic of an advanced stage of the disease. The vasodilatation test usually shows organic occlusion together with associated vasospasm. Occasionally we note evidence of associated pathologic changes involving vessels of the body, such as cerebral, coronary and visceral arteries. In the older age groups arterio-

sclerosis with calcification may also be present, making a definitive diagnosis sometimes quite impossible

Very often in this disease, in contrast to arteriosclerosis, the pulses at the wrist are also diminished or absent, but it can usually be differentiated from Raynaud's disease by the fact that the latter is unusual in males and rarely produces obliteration of the pulse. Thrombophlebitis is of the superficial veins and does not interfere with arterial circulation

Treatment again stresses hygienic care of feet and skin, in order to protect the individual against the development of open lesions and possible subsequent amputation. As stated before, the use of tobacco is absolutely forbidden and patients are thoroughly warned as to possible dire results therefrom. This attitude is taken after observing so many dramatic clinical responses within one month following the discontinuance of this habit. Efforts to produce vasodilatation by the use of heat in one form or another is recommended. The basal metabolism is usually checked and if found low thyroid substance is administered. Insulin free extracts of pancreas decrease the severity of claudication in some patients and their employment seems worthwhile. A dose of 2 cc is administered intramuscularly twice weekly for six weeks as a clinical trial.

The open lesions that occur in this disease result from insignificant trauma. This may be pressure from a constricting shoe, pressure from an ingrowing toenail, or the result of cracking of the skin where fungus disease is present. Solutions of potassium permanganate are valuable to control infection and reduce the action of the fungus. Fuchsin paints are most helpful. These lesions heal slowly, and seldom, without sympathectomy. Sympathectomy should be preganglionic in type, removal of the second and third lumbar ganglia being the operation of choice in the male, and the first, second and third in the female. Bilateral removal of the first lumbar ganglion in the male interferes with the ejaculatory mechanism. Temporary interruption of the sympathetic effect by paravertebral block or epidural anesthesia frequently gives evidence of the extent of spasm present and may give the patient enough symptomatic relief to produce an optimistic approach to sympathectomy.

Gangrene may progress rapidly after its inception. It may or may not be associated with infection. If the gangrene is confined to a small patch without involving the circumference of the digit, it will often demarcate and separate after sympathectomy. If the entire circumference is involved sympathectomy will improve the chances of healing by primary closure after amputation. This should be done if no infection is present.

In the thromboangitis obliterans group of patients, the already present extensive collateral circulation may be utilized by overcoming the

spastic element, thereby permitting a more conservative type of amputation in the presence of gangrene. This state of affairs may be contrasted with the generalized circulatory impairment noted in the arteriosclerotics, in whom more extensive amputation is required. Because of the younger age group involved, sites of amputation should be more carefully considered. Below-the-knee amputations are indicated wherever possible and preservation of part of the foot, particularly in young males, is important. It is often possible for a man to earn his living more advantageously with the use of his own leg than with a prosthesis. It is less satisfactory for a young woman to wear a prosthetic shoe where a portion of the foot is preserved, because of modern trends in foot-wear.

RAYNAUD'S DISEASE

Raynaud's disease is a disease of unknown etiology wherein the stimulus of cold or emotional response produces paroxysms of bilateral blanching or cyanosis of the digits. Local gangrene may result. This disease affects women chiefly in the second, third and fourth decades. It is not unusual to note an hereditary tendency. These patients are usually slender and of the "neurotic" type. The onset of the disease is usually not striking compared to the dramatic effects of a full-blown paroxysm. Often the initial attacks are so mild as to be forgotten. The patient frequently states that cold or excitement induces the paroxysms, or they will tell you of being bothered only in the winter time. Any number of digits may be affected, although the thumb is usually exempted. The terminal phalanges are more severely affected, but the cyanosis or blanching may extend proximally to involve adjacent areas of the palm. The digits feel numb and cold. The attacks may occur only on going out in the cold or they may recur frequently throughout the day. Many of the patients remain only mildly affected while a few show involvement of hands, feet, nose and ears. In the latter type of case, trophic changes such as pitting scars on the fingertips or small areas of local gangrene may develop. If scleroderma and atrophic arthritis become associated, extreme disability results. Necrotic areas with loss of substance of the fingertip, curving of the nails, x-ray evidence of fragmentation of distal phalanges, and thickening of the skin of the affected digits are diagnostic signs of an advanced state of the disease. Microscopically the capillaries of the skin itself are abnormal.

The diagnosis is obvious in a young woman complaining of paroxysms of symmetrical digital pallor induced by cold and who presents an absence of indications of occlusive arterial disease. The principal differentiations must be made between patients who have organic disease or anatomic abnormalities sufficient to produce irritability of the blood vessels or the nerves which control them. This rather secondary type of Raynaud's phenomena occurs in thromboangitis obliterans,

arteriosclerosis, cervical rib scalenus anticus syndrome, vibratory tool disease and arthritis of the spine

Treatment consists in correcting whatever medical conditions exist, such as anemia, hypothyroidism and focal infection. Protection against cold and the relief of mental stress proves helpful. Adverse working conditions should be remedied. If the condition is of more serious character, surgical interference is essential.

The surgery of Raynaud's disease is not entirely satisfactory. Sympathetic denervation of the upper extremity is more complex and less readily reached by operation than the sympathetics of the lower extremity. Before surgery is attempted, paravertebral sympathetic ganglion block should be done on the second, third and fourth thoracic ganglia. This should be accomplished without the production of a Horner's syndrome. Production of such a syndrome disconcerts the patient, who may feel that surgery will leave the condition permanent. The response to paravertebral ganglion block is usually prompt and subjectively gratifying to the patient.

Permanent sympathetic denervation may be satisfactorily accomplished through the anterior approach. In this procedure the scalenus anticus muscle is divided and not resutured. If a spastic muscle has contributed to the condition, it is thus corrected. At the same time a fibrous connection to the transverse process of the seventh cervical vertebra, previously unsuspected or simulating a cervical rib, may be removed. Ideally the sympathetic chain should be divided between the third and fourth thoracic ganglia and mobilized cephalad up to the first thoracic ganglion. No ganglia are removed. The divided chain is sutured to an intercostal muscle or the parietal pleura. The posterior approach involves rib resection and may prevent satisfactory mobilization of the sympathetic chain. The results of upper thoracic sympathectomy sometimes are not lasting. This may be due to an intrinsic spastic tendency of the vessels themselves rather than more central control.

After sympathectomy, the patient should expect the hand to remain warm, dry and pink in any type of weather or environment. Necrotic patches of the fingertips heal promptly. Stiffened fingers relax and normal activity may be resumed.

VENOUS THROMBOSIS

This condition generally may be classified in two types which actually overlap each other. The first type is *acute thrombophlebitis*. The second type is the more silent, obscure *phlebothrombosis*.

Thrombophlebitis frequently occurs in a bed patient who has had an acute infection, an operation or a recent obstetrical experience. It is characterized by elevation of the temperature and pulse rate. Pain

in the involved leg is common. Swelling occurs frequently. The leg may be hot to the touch or may exhibit some coolness or cyanosis. If the superficial veins are involved, palpation shows a tender, thickened vein with erythema of the skin overlying the vein. If the deep veins are involved, it is sometimes possible to palpate a thickened, tender vein in the inguinal region where the femoral vein crosses the ramus of the pubis. The pathognomonic sign is excruciating pain in the calf on forcible dorsiflexion of the foot. This is known as Homan's sign. Extent of the thrombosis may be determined by phlebography. It is interesting to note that this examination will sometimes show a thrombus lying free in the lumen of a vein, much in the manner one associates with phlebothrombosis. Pulmonary embolism is not unknown but is not very common.

Phlebothrombosis is believed to occur in the veins of the lower extremity where slowing of the venous return has taken place. It frequently occurs after surgery where the patient lies supine, reluctant to move, and with the knees partly flexed over an elevated portion of the bed. The presence of phlebothrombosis is not uncommonly suspected first after pulmonary embolus has occurred. Tenderness and pain are not the rule, and temperature elevation is not constant. Elevation of the pulse rate frequently occurs. Homan's sign may produce cramplike pain or evident discomfort, but the pain is not excruciating. Peripheral vasospasm usually does not occur.

The treatment of both conditions follows parallel lines. Sympathetic anesthesia will relieve the symptoms promptly in thrombophlebitis, but will not prevent pulmonary embolus or the chronic state known as "milk-leg." Anticoagulants may prevent progression of a thrombotic process and may ameliorate the severity of a pulmonary embolus, but they do not prevent but may reduce the edema and disability that occur after thrombophlebitis has been present.

Interruption of the involved vein wherever possible proximal to the disease process produces gratifying results. In this clinic it has been possible to determine the level for interruption by phlebography. With this aid the superficial femoral vein may be interrupted with impunity. If a thrombus is encountered, it is essential to apply suction to the proximal end of the vein and produce free bleeding. We have found that if this precaution is not followed, many of the unfortunate results of unsatisfactorily treated thrombophlebitis may occur. If this so-called thrombectomy is done, the results are much better. The operation may be carried out under local anesthesia, the swelling immediately begins to subside. We have not seen pulmonary emboli occur subsequent to ligation. It is known that if pulmonary embolus does occur after unilateral ligation, the unligated side usually is at fault. It is possible to ligate the deep veins as high as the venae cavae below the renal veins.

The postoperative results of ligation of the major vessels are amazingly satisfactory. These patients may need elastic support for as long as three months but usually can discard it permanently after that. Edema and ulceration are almost unknown. If they do occur, temporary or permanent sympathetic denervation may be of assistance.

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THE TREATMENT OF ACUTE RHEUMATIC FEVER

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ETIOLOGY AND INCIDENCE

DESPITE a tremendous amount of effort by the leading clinicians and laboratory workers of the world, the etiology and the effective therapy of rheumatic fever still remain one of the great challenges to modern medicine. For many years the streptococcus has been definitely suspected in the etiology, and with apparently good reason. A specific streptococcus has frequently been sought for, reported, and hailed with enthusiasm, only to have other laboratories fail in its confirmation. The Group A beta hemolytic streptococcus, however, still plays a prominent role in the theories of causation of the disease. Whether the condition is caused by an allergic response to the streptococcus, as some believe, by an ultramicroscopic body, as others feel, or by a factor yet to be identified, is a question left wide open for future investigations.

The prevalence of rheumatic heart disease, the crippling invalidism and early death resulting from it, make it a public health problem of large proportions. Insurance companies, recognizing its role in prematurely snuffing out the lives of many policyholders, have recently subscribed to a large fund for research in better methods of combating this serious disease. The public, alarmed by infantile paralysis, has subscribed much money for its treatment, but is not so concerned with the less dramatic and more chronic phases of rheumatic fever and rheumatic heart disease. It has been stated that rheumatic heart disease is one hundred times more fatal than infantile paralysis. When we remember the estimate that over one million individuals in the United States are affected by rheumatic fever and its sequelae, the magnitude of the situation can be appreciated. If some popular public official were to be stricken, a "March of Dollars" might result for extensive research in the cause and better treatment of rheumatic fever and its associated cardiac damage.

The contributing and precipitating factors in rheumatic fever are not within the scope of this paper, except for the planning of the convalescent care of patients. Climate has been known definitely to influence the incidence and recurrence of the disease. The tropics and extreme southern portions of the United States have a distinctly lower rate than the Middle Atlantic states and New England sections. As we come further north the percentage increases at a rate almost

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parallel with that of the degree of latitude Paul made an illuminating survey, in his careful study of the American Indian children on reservations, which seems to prove this fact. In a homogeneous and stable group the incidence of rheumatic fever and rheumatic heart disease was unusually high, 4.5 per cent in the northern group, 1.9 per cent in the intermediate area in New Mexico and Northern Arizona, and only 0.5 per cent in Southern Arizona.

Transporting convalescent children after a bout of acute rheumatic fever to a warmer climate has been a disappointing solution, for unless they can be kept there for a number of years the recurrence rate is not appreciably altered. On their return home they are usually subjected to their initial poor housing problem with crowding, dampness and renewed exposure to infection. It has been shown that reactivity sharply diminishes after puberty or after a period of five years has elapsed since the initial attack of rheumatic fever. Hence, because of economic dislocation it is rarely practical to keep them in a more favorable climate for the required number of years.

The varying incidence of rheumatic fever and rheumatic heart disease in different economic levels was indicated by a low rate in the expensive boarding schools in England, where the national rate is high. In eight thousand students at Yale the average incidence of rheumatic heart disease was 8.2 per 100 000. In private schools, however, the incidence was only 5.8 per cent as compared with 12.5 per cent in high schools. Wilson, who pointed out the increased incidence rate if one or both parents are rheumatic, has stressed familial tendencies in a genetic susceptibility of a definite recessive mendelian character. In the Army Air Corps, where rheumatic fever became a serious problem, it was noted that after exposure to streptococcal infection the disease occurred more often in groups with a history of rheumatic parents or siblings. The degree of positive throat cultures was rather uniform in the exposed group, but the incidence of rheumatic fever was low in the supposedly less susceptible individuals.

Jones has repeatedly emphasized the commonly observed fact that the first attack and reactivation of rheumatic fever are preceded by an infection of the upper respiratory tract. In an analysis of 750 cases in the House of the Good Samaritan in Boston, one of the largest hospitals for the care of cardiac children, 58 per cent of first attacks of rheumatic fever were preceded by an infection of the respiratory tract and 67 per cent of recurrent attacks. Even in those in whom no frank history or local evidence was detected, a large proportion showed serological evidence of recent streptococcal infection.

TREATMENT

The treatment of rheumatic fever is concerned with the acute active stage and the quiescent phase. The child who has had previous attacks

or who, having a rheumatic family background, is a potential subject, should be watched carefully in every episode of upper respiratory infection for early evidence of an active rheumatic state. An evening rise in temperature, languor, poor appetite, weight loss, irritability or change in disposition, abdominal pain, chest discomfort, or epistaxis should make one strongly suspect that an acute episode has developed. An elevated sedimentation rate and tachycardia out of proportion to the fever would be confirmatory findings, as would be electrocardiographic changes, such as a prolongation of the conduction time, or a high antistreptolysin titer. Skin manifestations such as erythema marginatum are also highly suggestive evidence of a rheumatic episode. Rheumatic nodules are considered to be evidence of a more severe attack and one that is likely to be longer in duration.

Absolute bed rest should be insisted upon until all evidence of activity has disappeared, whether it be weeks, months or years. A patient with active tuberculosis who goes to a sanitarium usually remains for six to twelve months. The analogy is apt, for the purpose of bed rest in both diseases is to render the process inactive. A highly nutritious diet of fruit juices, milk, eggs, green and starchy vegetables with moderate protein allowances and simple desserts is permissible unless the fever becomes high. Weight loss is frequent, ten to twenty pounds being not unusual. Adequate nursing care can be supplied at home by an intelligent mother if the patient is not hospitalized. Frequent warm sponge baths, alcohol rubs and powder will help to keep the skin in good condition and will add to the patient's comfort. Blankets instead of sheets and a flannelette shirt opening in the back will aid in the nursing care if there is much sweating. The sick room should be well ventilated, but the patient must be protected from drafts and chilling. Attention to elimination, adequate sleep, and appropriate types of occupational therapy are obvious requisites.

Drug Therapy—*Salicylates* are still the most valuable drugs in this disease. It is generally agreed that they are not curative, but they are analgesic, antipyretic and suppressive in their action. Unfortunately, they do not modify the disease process, but they do make the patient more comfortable, reduce fever and are valuable in aiding the absorption of transudates in the serous cavities. The pericardial effusions as well as the periarticular exudations seem to be distinctly benefited by this drug. The exudative phases seem to be shortened, but the proliferative changes, as in the heart valves, remain unchecked. Whether the Aschoff bodies in the myocardium are affected is highly problematic. Master and Romanoff concluded that salicylates did not prevent cardiac complications or shorten the duration of hospital stay.

Dosages of the salicylates and the question whether they should be combined with alkalis have been the subject of many reports. The ob-

ject is to obtain an optimum level of salicylates in the circulating blood, which is from 300 to 500 micrograms per cubic centimeter. Salicylates are rapidly absorbed from the upper gastrointestinal tract, and the addition of sodium bicarbonate reduces the gastric irritation which commonly accompanies large doses of sodium salicylate or acetylsalicylic acid.

Smull and others claim that simultaneous administration of equal amounts of sodium bicarbonate and sodium salicylate prevents the establishment of a serum salicylate level as high as can be obtained with sodium salicylate alone. Patients who are given sodium salicylate without alkalis and in whom a high level is reached show a definite fall in the serum salicylate level when sodium bicarbonate is given, but a return to the former level is obtained when the alkali is withdrawn.

A recent investigation by Caravati revealed some interesting observations on the toxicity of salicylates. One group was given salicylate intravenously and the other group equal amounts by mouth. The mean salicylate plasma level was approximately the same in both groups, but a higher percentage were nauseated when the drug was given by vein. Gastric analysis did not show any trace of salicylic acid when it was given intravenously, nor did the group treated orally when intubation was carried out six to eight hours after the final dose. Although the plasma level remained over 250 gammas when sodium bicarbonate was given with the salicylates to both groups, the salicylate level did drop appreciably, thus corroborating Smull's reports. The reason given was that the alkalis increased urinary salicylate excretion. The pH of the urine determines the retention of salicylates in the plasma, the lower the urinary pH, the higher the salicylate level in the blood. Gastroscopic examination made in twenty of the cases showed no abnormal mucosal changes even when large doses of salicylates were administered.

More moderate doses of alkalis seem to be adequate in controlling the nausea without affecting the desired salicylate serum concentration. Many clinicians are now prescribing 20 grains of sodium salicylate and 10 grains of sodium bicarbonate or 10 to 15 grains of aspirin with 10 grains of sodium bicarbonate, every four hours regularly day and night. If each dose is given with 8 to 10 ounces of water, nausea can often be prevented and the optimum blood level can be maintained. The oral method of salicylate therapy is preferable, and only rarely is the intravenous use of a 1 per cent sodium salicylate solution necessary. Coburn, who advises 10 gm. of sodium salicylate intravenously daily for fourteen days, reports striking results in suppressing the infection. He has had many followers of this regimen although toxic reactions of mental confusion, severe delirium, dyspnea and depletion of alkali reserve have been reported, a condition rare

with oral dosage. The rectal method is unsatisfactory, as salicylates are poorly absorbed per rectum.

The adverse effects of salicylates, notably increased blood coagulation time and the fall in the prothrombin content of the blood, have received much attention in recent years. The sedimentation rate and leukocyte count are not affected by salicylate therapy, but the hemoglobin and red blood count may be slightly reduced by long-continued administration of the drug. Some observers have found that in experimental animals and in man a hypoprothrombinemia developed when salicylates in the form of sodium salicylate or aspirin were given. This is similar to the changes found when a diet deficient in vitamin K was ingested. These blood changes were not found, however, or were prevented if vitamin K was administered simultaneously with the salicylates. A detailed study by the Rheumatic Fever Unit of the United States Naval Hospital, Corona, California, does show some effect of salicylates on the prothrombin content of the blood. But with the ordinary therapeutic dosage of salicylates there was no dangerous reduction found, and hemorrhages were not noted and seemed unlikely. In the clinical observation of the author over a twenty-five year period, no serious hemorrhagic manifestations were noted following moderately large doses of sodium salicylate with sodium bicarbonate. It has been repeatedly recorded that patients who have frequent nosebleeds before the recognition of an active phase of rheumatic fever and who are placed on salicylate therapy rarely have an increase in this annoying sign. It has never been a serious problem in the experience of my pediatric colleagues, but reports from some otolaryngologists have shown a tendency toward the development of late secondary tonsillar hemorrhages when aspirin is used after a tonsillectomy and adenoidectomy.

Aminopyrine occasionally gives striking results in the prompt reduction of fever and the acute symptoms. The dosage of 5 grains four to six times a day is frequently effective. The idiosyncrasy of some persons to this drug and the occasional case of granulocytopenia that results must be kept in mind and the leukocyte count carefully watched. The drug must be discontinued promptly if there is a reduction of the white blood cells below 6000.

Cinchophen and *neocinchophen* have also been used, as their physical effects are similar to those of the salicylates. *Neocinchophen* is preferable because it is less toxic, but cases of yellow atrophy of the liver have resulted from the use of both drugs. If administered, jaundice, urticaria and gastrointestinal symptoms must be carefully watched for as evidence of toxicity. The usual dosage is 15 grains every four hours.

Digitalis has no place in the routine treatment of rheumatic fever. If acute carditis is present, however, then congestive failure may de-

velop which will require the use of digitalis. This is best given in full doses orally with the tablets of the powdered leaf, which are now uniformly standardized. With the so-called "Philadelphia method" it is necessary to give 15 to 25 grains of the powdered leaf to digitalize the average adult. "Except in emergencies our usual routine is to give one and one-half grains four times a day for three days. Thus with a total of eighteen grains we approach full digitalization with little danger of toxic symptoms. From then on the daily dose is determined by the patient's circulation or the development of toxic symptoms. The average daily maintenance dose of digitalis is between one and one-half and three grains a day" (Stroud). It has been noted, however, that these patients, particularly children, are more sensitive to digitalis intoxication, and occasionally auricular fibrillation will develop as a sign of overdosage, with a return to normal sinus rhythm on its withdrawal. Thus, cautious use of this valuable drug in the active stage of rheumatic heart disease seems indicated.

Congestive failure may require additional measures for control, particularly if primary right sided failure develops. It has been suggested that this is due to an associated rheumatic pneumonitis which increases the blood pressure in the lesser circulation and throws a marked strain on the right ventricle. Theobromine seems particularly useful in this complication in younger patients. Diuresis can usually be accomplished by giving $7\frac{1}{2}$ grains of theobromine sodium acetate three or four times a day. Three grains of aminophylline three times a day may also be used for the same effect. These two preparations are best administered in enteric coated tablets to reduce gastric irritation.

If the xanthines and digitalis are not sufficient to reduce the edema, then mercurpurin may be given with distinct benefit. This should be given in 1 to 2 cc. doses intravenously every three to five days depending on the urgency of the failure syndrome. Its action is synergistically fortified by the administration of ammonium chloride in enteric-coated tablets in doses of 30 to 60 grains, depending on the age and size of the patient.

Oxygen Therapy.—Oxygen is of distinct benefit in congestive failure, particularly if rheumatic pneumonitis is present. It will relieve the dyspnea, cyanosis, and restlessness, and should be used as soon as these symptoms develop. It can be administered by a tent or preferably by a catheter into the nasopharynx. This reduces the amount of oxygen required, markedly simplifies the nursing care and avoids the claustrophobia that many patients develop when enclosed in an oxygen tent.

Other Drugs.—Because of the recognized relationship of streptococcal sore throat to the activation of rheumatic fever, the sulfonamides were immediately greeted as a possible curative measure. It was soon apparent, however, that they were in no way beneficial in the treatment of acute rheumatic fever but frequently were actually harm

ful It has been shown by the Rockefeller group and many other investigators that during the acute phase they are valueless, and their use should be condemned

Penicillin, again, was optimistically hailed as a wonder drug, but was found to be without demonstrable benefit This might be confirmatory evidence of the earlier theories of an allergic reaction in a susceptible individual whereby the streptococcus only plays the part of a "trigger" mechanism to set up the protean manifestations of the rheumatic state

SYMPTOMATIC TREATMENT

Symptomatic treatment of patients with active rheumatic fever is usually indicated Acutely inflamed joints rarely occur in children under eight years of age, but when polyarthritis is present, local measures can definitely add to the patient's comfort Complete rest is obviously indicated, and if prolonged will not lead to stiffness, as permanent joint changes do not occur in uncomplicated rheumatic fever Wrapping the inflamed joints in cotton, supporting them with pillows in a partially flexed position and using a cradle to support the weight of the bed clothes are comforting Splints are unnecessary, for the painful swelling is usually not long in duration Local application of a saturated solution of magnesium sulfate covered with rubber sheeting is used, but methyl salicylate is less troublesome and seems to be more effective A 10 per cent ointment or a 25 per cent solution of methyl salicylate can be used Mild heat applied locally with hot water bottles or electric pads is an additional soothing measure Codeine or even morphine may be required to control the extreme pain of this distressing phase

The red, hot, shiny, swollen, tender joints are fortunately less frequently seen than they were twenty to thirty years ago But is the percentage of heart involvement decreasing? The oft-quoted saying of Laseque, "It licks the joints, pleura, and meninges, and bites the heart" still seems to be appropriate today

INACTIVE PHASE

It is difficult to determine when the active stage has subsided and the quiescent phase and recovery have begun Certain criteria have been established as to when it is safe to relax the stringent rules for bed care and begin a rehabilitation program The following postulates have proved useful in arriving at this decision

- 1 A persistently normal temperature (After salicylates or antipyretics have been omitted)
- 2 A pulse rate normal for the patient's age
- 3 A normal blood sedimentation rate

4. No rheumatic nodules
5. No choreiform movements
6. No signs of congestive failure.
7. No serous membrane involvement
8. No intercurrent disease or infection
9. No electrocardiographic abnormalities

Gradual resumption of the "out of bed" stage can now begin. The reaction of the pulse rate to sitting up in a chair, walking ten steps, etc., is a useful gauge for the permissible increase in privileges. Fatigue must be avoided at all times.

Foci of infection can be removed during the quiescent stage, but removal of infectious foci is contraindicated during the active phases. Teeth and tonsils may require removal, but this should not be done if it is possible to wait for at least six to twelve months after all evidence of activity has cleared. Sulfathiazole should be given for three days before and two days after the removal of infected tonsils and teeth to prevent the possible superimposition of a subacute bacterial endocarditis on a previously damaged heart.

Vaccines and serums have been used extensively in the past with disappointing results. Further investigations may possibly reopen this field, but at this time they seem to be of little value.

Blood plasma has also been tried, but has caused a flare-up in the active phase so that its use is contraindicated. Whole blood transfusions are occasionally given, but rarely is the secondary anemia of sufficient degree to require other than hematinic measures.

Fever therapy has been used particularly in chorea. Sutton has advocated artificial fever therapy by the intravenous use of a triple typhoid vaccine, or by the diathermy machine or the Kettering hypotherm. She concludes that the severity of the choreiform movements is diminished, the course of the hospital stay shortened, and there was a beneficial influence on the course of the carditis. If vaccine is used, the initial dose should be fifteen to twenty five million organisms intravenously, and later doses should be increased to cause a fever reaction of 102° F or higher.

Iron is usually necessary because most persons with active rheumatic fever develop a secondary anemia. The ferrous salts are the most effective and best tolerated, either in the tablet form or in a liquid preparation for younger children.

X ray treatments over the myocardium and cervical sympathetic ganglia have been advocated and tried out by several groups with inconclusive results except for the possible psychogenic effect.

Physical therapy is contraindicated during the transudative stage. Obviously, with acutely inflamed joints motion and manipulation will add to the discomfort of the patient as well as aggravate the inflam-

mation In older patients it can be mildly beneficial in the less acute phases to prevent muscle weakness, etc

Climatotherapy, as discussed before in its possible role in etiology, can be of value if carefully controlled and its limitation recognized A warm, dry climate with gradually increasing exposure to the sun in the subsiding or convalescent stages may be of some benefit Extreme exposure to the sun has proved harmful and should be carefully avoided The incidence of hemolytic streptococcus infections has been shown to be definitely less in the Army and Navy camps in the warmer and subtropical regions, where the dangers of exposure to reinfection and of reactivation of the rheumatic state are reduced The change in climate is, of course, not curative and confers no immunity, but merely removes the individual temporarily from the provocative infection

Sulfonamides—The question of avoidance of infection is an important one, and many studies have been made We do not have the final answer as to the best method to prevent such infections, for there is no unanimity of opinion as to the ideal and safest or most effective procedure We know that sulfadiazine throughout the year has reduced streptococcic infections by 80 per cent Another group reported by Thomas and others showed a marked reduction of a beta hemolytic streptococcus in pharyngeal cultures when given sulfanilamide, in contrast to the control group None of the sulfa-treated patients had a major attack of rheumatic fever or acute streptococcic infection, while the untreated group had fifteen major attacks of rheumatic fever, and five others developed suspicious rheumatic manifestations Many omit sulfonamides during the summer months as the incidence of "colds" and respiratory infections is sharply diminished and the likelihood of exposure markedly reduced If this regimen is carried to its logical conclusion, sulfonamides should be used for at least five consecutive years to prevent, if possible, reactivations during the period when recurrence is most likely to follow

Bauer has advocated sodium salicylate and sodium bicarbonate for one week of every month instead of the sulfonamides In a large boarding school he found that the salicylates gave a better end result after several years' observation than did a similar group given sulfonamides daily

Some physicians who treated rheumatic fever in adults in the Army and Navy in World War II found that prolonged bed rest is unnecessary and may be harmful Undoubtedly there are occasional cases of cardiac neuroses fostered or fixed by protracted bed care in children or adults with rheumatic fever It is easier, however, to overcome such a complication than to treat a heart severely damaged because of too early relaxation of restrictions, and many of us prefer to risk a neurosis

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SYMPOSIUM ON CLINICAL PATHOLOGY

FOREWORD

In presenting this Symposium on Clinical Pathology an attempt has been made to bring together a number of clinics on subjects in which laboratory studies play an important diagnostic role.

Clinical Pathology has become a science that embraces more than bedside medicine and more than the abstract performance of laboratory tests. It involves an understanding of the underlying physiological disturbances and might be more properly referred to as "clinical morbid physiology." It is not enough in the study of a disease to know that the results of a laboratory examination are negative or positive or fall within or without accepted normal limits. It is frequently important to know the stage of the disease or the duration of illness; it is necessary to interpret the results of laboratory examination with a full knowledge of the special variation of signs and symptoms in a certain disease, and also to know what complications may or may not exist.

The matter of collection of specimens also deserves special consideration. The period of illness, the proper preparation of the patient before collection of the specimen, the handling of the specimen between the time of collection and laboratory examination, all become matters of greatest importance if helpful information is to be derived from the examination.

Lastly the selection of laboratory tests which are most likely to reveal useful information must be made with a thorough understanding of the disease and laboratory procedures if the patient is not to be exposed to unnecessary expense and inconvenience, and the laboratory to wasteful effort.

Only the clinical pathologist can be particularly fitted for making decisions in all of these matters. He is or should be well informed in the clinical manifestations of disease and by special training is familiar with the requirements for the collection of the proper material for examination at the right time and under the proper circumstances. His experience has taught him the limitations of laboratory methods and the circumstances under which those laboratory methods are dependable. Decisions on these matters are no longer any more the obligation of the general practitioner or the internist than would be the conduct of a surgical procedure by these same men.

It is fully appreciated, nevertheless, that the surgeon and the internist alike wish to know something of the reason for and the methods of evaluating laboratory studies, and it was in the hope of illuminating the subject from such an angle that this symposium has been prepared

FRANK W KONZELMANN

Consulting Editor

PRESENT DAY METHODS IN THE DIAGNOSIS OF SYPHILIS

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THE recent great advances in the therapy of syphilis have not lessened the need for accurate diagnosis. In fact, the uncertainties attending the evaluation of new modes of syphilotherapy demand even greater than usual precision in diagnosis as well as a reliable gauge of the effectiveness of treatment. The recent advances in the means of diagnosing syphilis have not been in the direction of the development of new tests, but rather toward standardization, quantitative serologic techniques and better interpretation of results. Specifically, the efforts of the past twenty five years have shown the relative value of complete history and physical examination, it has established the usefulness of the delayed darkfield procedure, the utility and practicality of the lymph node puncture technic, the relative uselessness of spirochetal stains and a variety of advances in the field of serology listed in Figure 156.

In addition advances in the interpretation and classification of cerebrospinal fluid results have afforded a reliable index to the treatment and prognosis of neurosyphilis. For details of procedures used in the diagnosis of syphilis, larger texts such as *Modern Clinical Syphilology*¹ should be consulted. In this review we shall present certain of the practical aspects of the problem of interest to the clinician, especially those dealing with the darkfield, the blood serologic tests and the cerebrospinal fluid.

THE DARKFIELD EXAMINATION

In the darkfield examination for *Spirochaeta pallida* we have a most useful diagnostic aid, but in inexperienced hands it is a source of misleading

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Fig 156

TOPICAL SUMMARY OF SEROLOGIC PROGRESS SINCE 1932

- 1 Better comprehension of immune body and syphilitic reagin relations
- 2 Light on the specificity of tests for syphilis by the use of a spirochetal antigen (the Reiter and other antigens)
- 3 The presence of syphilitic reagin demonstrated in apparently nonsyphilitic human and animal blood
- 4 Development of methods (Lund) for identifying minute amounts of syphilitic reagin An investigative method
- 5 Use of reagin titration in diagnosis and treatment
- 6 Emphasis on quantitative serologic technics
- 7 Recognition of "zone" reactions as sources of nonagreement in some serologic tests
- 8 Passing of the provocative procedure
- 9 Continued controversy on contradictory and conflicting serologic results
- 10 Testing of specificity and use of ultrasensitive procedure (screen, presumptive, exclusion and elimination tests) to *exclude* syphilis from a diagnosis
- 11 Increasing demonstration of the margin of error of the positive serologic reaction—expanding field of *biologic* false positives
- 12 Development of procedures for differentiation of syphilitic from nonsyphilitic positives—verification tests
- 13 Standardization of American serologic laboratory practice—approved tests, approval status based on extensive cross-checks of laboratory performance Results of conferences Approved methods of reporting
- 14 Rivalry between newer simplifications and "approved" or "standard" tests
- 15 Development of state laboratory systems National possibilities
- 16 Mass serologic testing and routine use of a case-uncovering mechanism
- 17 The enactment and influence of blood-testing laws
- 18 Definition of blood test and infectiousness relationships
- 19 Relation between reagin content of the blood of mother and newborn child
- 20 Declining clinical importance of seroresistance (fixed positive)
- 21 Initiation of research into the nature of the syphilitic reagin by chemical and physical serum fractionation methods

From Modern Clinical Syphilology¹

information Because one may with this method find the spirochetes before the blood serologic reactions are positive (seronegative primary phase), treatment may be started with the greatest assurance to the patient of cure A patient treated in this seronegative phase of syphilis removes a dangerous source of infection from the community Thus, at one time, the darkfield procedure leads to personal and to public health benefits Unfortunately there are serious limitations to the wide applicability of this statement In the first place, darkfield examination is rarely used or, if used, on lesions which are too old, in sites where spirochetes resembling *Spirochaeta pallida* abound (e g, the mouth), the yield of reliable diagnostic information is indeed small

In recent years all physicians of many communities have had darkfield facilities placed at their command This is the result of the avail-

ability of the delayed or deferred darkfield examination by which is meant the examination in a definitely designated laboratory of specimens about twenty four to forty eight hours after their collection in capillary tubes from a suspected source. While this is not as efficient a procedure as the direct or immediate method it is an excellent means of widening the distribution of darkfield facilities.

Another darkfield procedure, lymph node puncture is one which has been given high acclaim by both military^{2, 3} and civilian syphilologists.

Fig 157

ILLUSTRATING TYPE OF CASES IN WHICH DARKFIELD EXAMINATION OF LYMPH NODES IS OF VALUE

I. Inaccessible lesions

- A Intraurethral chancres.
- B Lesions obscured by phimosis or paraphimosis but palpable
- C. Old involution chancres but still presenting induration to palpation. If lymph nodes are enlarged, it is frequently easier to aspirate them than to aspirate the base of the lesion and at this stage the chances of finding *T. pallidum* are probably greater in the lymph node.
- D Secondary syphilis with moderate enlargement of lymph nodes and no residual of the primary lesion no mucosal lesions and no suitable secondary lesions for darkfield. Done to save time and to institute therapy as soon as possible i.e., before the return of blood serologic results †

II. Accessible lesions

- A. Chancres of long duration upon which the local darkfields are repeatedly negative
- B Dirty painful, secondarily infected chancres Easier to do than local darkfield much more accurate and less time consuming
- C. All chancres or secondary lesions within the oral cavity—especially chancres of the tonsils. In such cases, nonpathogenic mouth spirochetes simulating *T. pallidum* are eliminated.

* It is assumed that in each case the nodes must be sufficiently enlarged to make their aspiration feasible

† Loveman and Morrow's only cases of error (negative results) fell in this group but they still feel it to be of value in selected cases

Adapted from Loveman and Morrow *Am. J. of Syph., Gonorr. & Ven. Dis.* 28 (1):44-56 (Jan) 1944.

gists This consists of removal by syringe and needle of a little of the tissue juice of an enlarged lymph node and examining it with the darkfield in the usual way. Lymph node puncture is a specific procedure since no organisms resembling *Spirochaeta pallida* are to be found in lymph nodes in usual practice. Figure 157 shows the type of cases in which darkfield examination of lymph nodes is of value.

A further means of facilitating the early darkfield diagnosis of syph

is which deserves emphasis and commendation, is that devised by Friedman⁴ for the darkfield examination of pus for *Spirochaeta pallida*. This is a simple method in which the pus collected in capillary tubes is centrifuged for ten minutes at 1000 revolutions per minute and the supernatant fluid is examined in the usual manner by the darkfield method. By this technic one has the earliest and often only means of diagnosis of the intraurethral chancre which may be masked by gonorrhea. This is especially important in this penicillin era when for the first time one drug is effective against both syphilis and gonorrhea.

STAINS FOR IDENTIFYING SPIROCHAETA PALLIDA

Staining methods for the identification of *Spirochaeta pallida* in smears or tissue are at best unsatisfactory. The organism is difficult to stain and this is indicated by the host of staining methods introduced in recent years. Furthermore, even if the organism were well stained, one has to rely upon a static situation for identification. The graceful regular movements of the organism, the regular contour of the spirals and other data supplied by darkfield observation of living spirochetes are lost in the stained preparation.

THE ELECTRON MICROSCOPIC DEMONSTRATION OF SPIROCHAETA PALLIDA

The demonstration of the morphology of *Spirochaeta pallida* by the electron microscope can hardly be classed as a clinical diagnostic method. The studies of this organism by this means by Morton and Anderson⁵ and by Wile, Pickard and Kearney⁶ open a new avenue for a positive identification of the spirochete, which in turn may lead to simplification of clinical procedures.

THE SEROLOGIC TESTS FOR SYPHILIS

Among the important advances in serology in the past twenty-five years there are some which deserve more emphasis for the practitioner. In this discussion we shall cover a few of the more important ones: the relations of the syphilitic reagin to immunity, the quantitative serologic test, relation between reagin content of the blood of mother and newborn child, the provocative procedure, biologic false positive reactions and methods for identification of these reactions, standardization of tests and laboratory practice and mass serologic testing.

The Relation of the Syphilitic Reagin to Immunity—The original concept of the Wassermann reaction as a specific antigen-antibody reaction has undergone periodic waves of alternating support and denial. The recent work of Beck,⁷ Kolmer and his group,⁸ and of Eagle and his associates^{9, 10} has tended to indicate that the

serologic tests for syphilis do seem to have some of the qualities of an immune body antigenic reaction but the degree of specificity involved still remains a matter of disagreement. Work with the spirochetal antigen ("palligen") revived by Gaehtgens¹⁰ Erickson and Eagle¹¹ and Kolmer and his associates⁸ has unfortunately not supplied the answer to the specific versus nonspecific reaction question. Kolmer and his colleagues believe the syphilitic antibody is distinct from the syphilitic reagin. They seem inclined to regard the reaction as in part due to natural group spirochetal antibody contained in some animal and human blood, as well as that produced in syphilis which reacts with cultivated *Spirochaeta pallida* as well as with other spirochetes. This spirochetal complement fixing antibody is increased in syphilis and other diseases such as malaria and leprosy. Eagle and Hogan¹² have maintained that the two are identical. When this question is put to the test in employing the spirochetal antigen to differentiate true from false serologic reactions one is left with the distinct demonstration that antigens prepared with cultures of alleged *Spirochaeta pallida* are capable of giving a varying percentage of nonspecific or falsely positive complement fixation reactions with the serums of nonsyphilitic individuals. For example in a total of 36 255 tests employing "palligen" these have varied from 0.4 to 3.4 per cent.¹¹ In the 1941 Washington Serology Conference¹² the tests on the blood employing spirochetal antigens resulted in a definitely lower specificity than the usually employed complement fixation or flocculation procedures. It must be stated, however that when used on cerebrospinal fluid where there is little or no natural spirochetal complement fixing antibody (Kolmer) the spirochetal antigen tests gave a high degree of specificity. Accordingly Kolmer's conception of the separate identity of reagin and syphilitic immune body seems to be the acceptable interpretation.

Quantitative Blood Tests for Syphilis—In the attempts to improve the significance of serologic testing, wider use is being made of the quantitative serologic procedures.^{13a, b, c} For routine work, however the determination and reporting of the serologic titer is still somewhat confusing to the practitioner. For following the effects of modern intensive treatment, for anticipating relapse for the diagnosis of syphilis in the infant and for establishing true seroresistance, quantitation of serologic reactions is indispensable. For the differentiation of true from false serologic reactions and for gauging the activity of the syphilitic infection the quantitative procedure is far from reliable. In all cases where this modification of serologic performance is employed, it must be remembered that the various results are of significance as a basis for comparison only when they are obtained by an identically similar testing technic.

The quantitative procedure may be carried out by at least three

methods One may determine the smallest amount of antigen necessary for a positive reaction, the least amount of complement required, or the serum may be diluted until it no longer yields a positive reaction Chiefly for economic reasons the third technic, serial dilution, is most widely used In this method the reagin titer is reported in units and represents the highest dilution of serum giving a positive result For example, if the 1:32 dilution is positive and the 1:64 dilution is negative, the titer is reported as 32 units In view of the daily variation in sensitivity,¹³ it must be emphasized that the difference between 1 or 2 dilutions (e g, 32 or 64 units) is not as significant as the numerical representation would seem to indicate A fairly strong reaction is 256 units but the range may vary from 0 to 1600 or more units If the quantitative Kahn test is used, the units represent four times the maximum dilution of the serum giving a positive result, since incomplete flocculation in undiluted serum is recorded as 1, 2 or 3 units Recently Boerner and his co-workers^{15a, b, c} have developed a quantitative fixation of complement, a quantitative macroflocculation test and a method of grouping and classifying serologic reactions for syphilis, but it is too soon to judge the value of these procedures

The Quantitative Reactions in Early Syphilis.—Contrary to the opinion of some syphilologists, we believe that the quantitative procedure is of limited positive value in the diagnosis of suspected primary syphilis It is not justifiable to consider a genital lesion, dark-field negative for *Spirochaeta pallida*, in the presence of a rising serologic titer as entirely proven primary syphilis However, as a working rule, a sharply rising reagin titer is frequently observed in recently acquired syphilis, a more or less stationary titer suggests the possibility of an infection of some duration and a falling titer without treatment intimates the possibility of a biologic false positive reaction It should be reemphasized that while biologic false positive reactions are often of low titer, the earliest phase of syphilis may likewise have a low or negative titer, or a rising titer *The quantitative serologic procedure is not a substitute for careful darkfield examination of a suspected primary lesion*

The quantitative procedure is an indispensable gauge for estimating the efficacy of treatment in the case of intensive therapy of syphilis with the arsenicals or penicillin In the case of *qualitative* tests, the physician has no way of determining whether a positive result persisting over a period of time is really becoming less strong, stronger or stationary In this event he has no means of determining, until it is too late, whether treatment is effective or the patient is threatened with an impending clinical relapse which is often, but not always, preceded by a definite rise in titer Emphasis must again be placed on the fact that a small difference between two determinations of the serologic titer need not be an indication of rising titer or of impending relapse

Quantitative Tests in Seroresistance—The diagnosis of seroresistance or "Wassermann fastness" may be definitely established only by the quantitative technic. In such a case the ordinary test reveals consistently positive results, while the quantitative technic may indicate falls in titer of great magnitude. In the truly Wassermann fast case the titer remains more or less stationary over long periods, in spite of what would ordinarily be considered adequate treatment.

The Quantitative Blood Test in Congenital Syphilis—Because a positive cord blood of the newborn infant, as well as the early serologic positive reactions of the infant of a seropositive mother, may represent a transfer of syphilis reagin from the maternal to the fetal circulation, *a single positive blood test cord or otherwise, cannot be accepted as diagnostic of infantile congenital syphilis*.

The use of serial quantitative titered blood serologic tests has made it possible to show that, if the infant is not syphilitic, the concentration of syphilis reagin in its blood stream is never more and often considerably less than that of the maternal blood stream. *The syphilis reagin will gradually disappear from the normal infant's blood stream after some days or weeks.* If the maternal blood serum reagin content, and hence the infant's has been high, the infant's titer will decrease rapidly at first, but after it falls to 1 or 2 units it may persist at this level for many days.

If the infant, on the other hand, has syphilis in rare instances presumably when infection has occurred early in pregnancy and the infection is well advanced at the time of birth the infant's blood serologic test may have a significantly greater titer of reagin than that shown by the maternal blood. This is considered to be of diagnostic significance. More commonly, however, presumably when the fetus is infected closer to term, the infant's titer will be in the same magnitude as the maternal serum reagin content for some days or weeks postnatally and may again rarely decrease even to the vanishing point, only to increase again rapidly and steadily, as the disease becomes clinically manifest.

Ingraham Shaffer Spence and Gordons¹⁶ experience has shown that more than one half of the seropositive nonsyphilitic infants had negative serologic reactions by the age of one month but about 3 per cent persisted into the second month of postnatal life. Occasional cases have been observed in which complete seronegativity is not reached until from seventy to ninety days. In the sole instance in which the reagin titer of the infant's serum was significantly greater than that of the mother's at birth, the mother's serum contained units and the infant's 64 units.

The quantitative titered blood serologic test has considerably value in eliminating the nonsyphilitic patient with positive serologic reactions, by detecting a rapidly falling titer than it has in est-

ing an absolute diagnosis in the study of the truly syphilitic patient. Our experience has been somewhat in accord with Christie's,¹⁷ in that syphilitic infants with positive serologic reactions at birth seldom seem to show a rapid or significant increase in the titer short of an observation period of one month to six weeks (Fig 158)

The Provocative Procedure.—Many observers believe that a rise in the titer of syphilitic reagin occurs in syphilitics and in apparently normal persons, following the induction of antisyphilitic treatment, particularly with an arsenical and penicillin. The finding of syphilitic

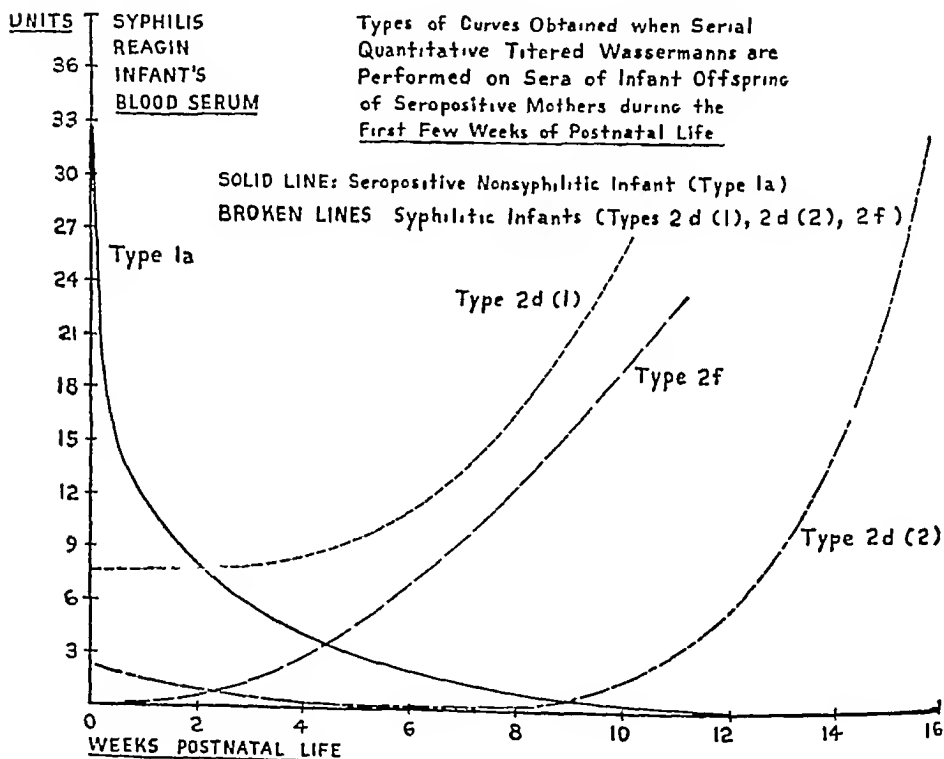


Fig 158—(From Modern Clinical Syphilology)

reagin in the blood of normal persons, its increase under nonspecific influences such as intercurrent infections, its increase following the very procedures employed to cause its increase in syphilitic individuals, and the demonstration that serial tests on any blood are subject to marked variation, especially in borderline degrees of positive serologic reactions for syphilis, have all weakened confidence in the test to the point where it can no longer be recommended for general use as a diagnostic procedure. On the other hand, that a rise in reagin titer does occur as a species of Herxheimer-like flare reaction in syph-

ilis occasionally justifies the expert, thoroughly familiar with the interpretative pitfalls involved, in using what might be called a provocative procedure as an aid in diagnosis

Biologic or Nonspecific False Positive Reactions to the Tests for Syphilis.—Since the Wassermann and flocculation procedures have been shown to be nonspecific, it is not strange that with the wider use of the tests, the problem of false reactions has become acute. Although such reactions were previously recognized, it is only recently that much real attention has been paid to the subject. In spite of the immense interest and study one can say that *as yet no test exists which will differentiate true from false reaction to the serologic tests for syphilis*. The practitioner must depend upon the various procedures we shall outline for deciding on individual cases.

Biologic false positive reactions are the result of a number of factors which predispose the individual to develop them. They have been summarized by Rein and Elsberg¹⁸ as (a) *serologic reactors* (some individuals are more apt to develop the reactions than others), (b) *type of the nonsyphilitic disease* (malaria and leprosy frequent causes) (c) *incubation period for the development of false positive serologic reaction* (usually seven to twenty one days), (d) *number of tests employed in the serologic battery* (more tests employed, more false reactions detected) (e) *types of tests* (f) *intervals of testing* (more frequent testing, more false positive), (g) *duration of false positives* (usually negative in three to four months).

False positive reactions have been noted in a host of circumstances in health and disease. The variety of diseases shown to produce false reactions to the tests for syphilis is increasing almost daily.^{19a to e} Extensive lists of the processes accompanied by false reactions may be found in the reviews by Davis²⁰ and by Beerman,²¹ or in *Modern Clinical Syphilology*.¹ The cause or causes of their occurrence are unknown and would yield little for the practitioner if they were detailed here. *As yet no verification procedure has been devised which will differentiate true from false reactions* although excellent efforts have been made in this direction —a to f.

A recent case will illustrate the complexities of this problem

A. H., a white male veterinarian aged 28. In 1937 had acne vulgaris. He had septicemia late in February 1946 for which he received 1 000 000 units of penicillin (intramuscularly and orally). Question of brucellosis was raised but no skin tests were made. In March 1946 while doing rectal procedures he developed an evanescent rash on forearms. He had had no sexual intercourse since early 1943. Preinduction serologic examination in November 1943 gave negative results. He donated blood to the American Red Cross in March 1944. He denies primary or secondary syphilis. No physical evidence of syphilis was disclosed at any time during the study.

Date	Laboratory	Results
3/23/46	1	Wassermann pos, Kolmer pos, Mazzini pos., Kline pos
3/29/46	2	Wassermann neg, Kahn pos., Eagle pos
3/30/46	3	Kolmer neg, Kline pos
4/ 1/46	4	Over 4 flocculation units (pos)
4/ 1/46	5	Kolmer pos (64 units), Kline pos (128 units)
4/ 8/46	5	Kolmer pos (128 units), Kline pos (256 units), Eagle pos
4/ 8/46	4	Class 10 (pos)
4/15/46	5	Kolmer pos (64 units), Kline pos (256 units), Eagle pos
4/29/46	5	Kolmer pos (64 units), Kline pos (128 units)
4/29/46	4	Class 2 (neg)
5/ 6/46	5	Kolmer pos (2 units), Kline pos (16 units), Eagle pos
5/ 6/46	4	Class 2 (neg)
5/20/46	5	Kolmer neg, Mazzini neg., Kline neg 1 plus
5/20/46	4	Routine Wassermann neg
6/10/46	5	Kolmer neg, Mazzini neg, Kline neg
6/11/46	4	Class 1 (neg)
	Laboratory 1—A state laboratory	
	Laboratory 2—A private laboratory	
	Laboratory 3—A city laboratory	
	Laboratory 4—A research laboratory	
	Laboratory 5—A syphilis clinic laboratory	

Although the quantitative testing of this patient's blood has yielded a curve of rising titer which reached its peak about four weeks after a "septicemia" and which had definitely fallen to negative by three months the question of what 1,000,000 units of penicillin for the "septicemia" did to the serologic reactions must be considered. We believe the rise after penicillin is just what one would expect in the case of syphilis developing in a patient treated with small doses of penicillin for gonorrhea, but the subsequent spontaneous fall to negative is not in accord with the findings in patients who have developed syphilis under these circumstances. Accordingly, we feel that this man had a false positive reaction.

Principles Suitable for Routine Blood Testing—This case raises the question of what to do in the event the physician is interested in routine blood testing. Stokes and his colleagues²³ have presented a set of principles suitable for such practice.

1. Mere routine blood serologic testing, without examination or questioning, will certainly lead to a proportion of nonspecific positives that will be expensive and serious for the individuals concerned, and a source of error in statistical evaluation. The nonspecific positives obtained may run as high as 50 per cent, depending on the selection of case material, on the serologic procedures employed and on the rating given partial positives.

2. The best laboratories will give nonspecific positive serologic reports, but they will be fewer if a complement fixation technic is used.

and more easily interpreted if a quantitative precipitation test is matched against a quantitative fixation of complement test, as in the Boerner classification procedure

3 The drawing of blood for serologic testing should be preceded or accompanied by

(a) Questions

Have you had or been treated for syphilis or gonorrhea? (Ask again and again)

Have you had malaria?

Have you had within a month a fever, cold, grip, pneumonia severe sore throat?

Have you had any preventive inoculations within three months (tetanus, typhoid smallpox vaccination)?

Have you had blood tests before? Results?

(b) At least a once-over physical inspection

Pupils

Rashes (semistripped or stripped)

Oral mucosae and teeth.

Genitalia if possible or indicated

Tibias

Signs of intercurrent infection

(c) Temperature, pulse, respiration Auscultation of heart and lungs if above normal.

4 Nonspecific positives may be suspected if

(a) There is a weak positive or doubtful serologic test result.

(b) There is a conflict between precipitation and complement fixation results

(c) Even though a repetition is positive the titer remains low and is fluctuant.

(d) There is a decline in titer to negative on weekly tests for one to three months, without treatment.

5 A syphilitic positive should be suspected if

(a) The original and subsequent reaction are persistently of high or even low titer

(b) There is clinical or anamnestic evidence of positive weight.

(c) The spinal fluid, after the aforementioned blood checks, is definitely abnormal, not alone with respect to serologic tests

The occasional occurrence of false positive reactions should not lead to wholesale condemnation of the serologic tests for syphilis. The following quotation from Harrison and Osmond⁴ is a sound evaluation of the present status of these procedures

In 1918 the Medical Research Committee (now the Medical Research Council) Committee on the Standardization of Pathological Methods said

"In the opinion of the Committee there is no process of biochemical diagnosis that gives more trustworthy information or is liable to a smaller margin

of error than the Wassermann test when it is performed with completeness and with proper skill and care "

This is probably as true today as it was when written a quarter of a century ago, but it is equally true that no group of tests has given rise through unskillful performance and through inadequate appreciation of their limitations, to more unhappiness than have the serum tests for syphilis

Standardization of Serologic Performance.—The physician has a great desire for 100 per cent specificity and sensitivity in his serologic reports. Agreement on positive results in tests may vary from about 78 to 100 per cent. Disagreements may be expected under many circumstances, even when the same specimen is examined repeatedly by the same and different tests, at the same time (split specimens) or serially over a period of time. In view of this disagreement, which great effort has not entirely eliminated, constant checking of serologic performance and approval of laboratories is being carried on at local, state and national levels. The results of these attempts of standardization have led to the following statement

The specificity of serologic tests is in general more important than their sensitivity. Specificity should be practically 100 per cent, and in laboratory grouping and approval status, a specificity rating below 99 per cent on 200 test specimens or 98 per cent on 100 specimens should lead to the temporary exclusion of the test from the approved list until such time as modification re-establishes a rating for it of 100 per cent. [On the other hand] an approved sensitivity rating shall be not more than 20 per cent below that of the control laboratory in cases of late or treated syphilis, and within 1 per cent of that of the control laboratory in cases of untreated and secondary syphilis

It is pertinent at this point to mention for future reference the isolation by Pangborn²⁵ of the substance cardiolipin from beef heart and the standardization of other elements employed in the serologic tests. Rein and his co-workers²⁶ have re-emphasized that cardiolipin antigen (cardiolipin 0.2 per cent and lecithin 1.3 per cent) may be successfully adapted to microflocculation slide test for the serodiagnosis of syphilis. Further studies are needed to ascertain the place of cardiolipin in general serology.

Mass Testing—Mass serologic testing for the determination of the presence and prevalence of syphilis in population groups has become an established public health and military practice. The value of the routine serologic test in every medical examination and in large groups of people (as in industry) is attested by a large series of reports in the literature. For example, in one recent report by Zeller-mayer²⁷ analyzing 5000 inductees in whom positive serologic reactions for or a definite history of syphilis were found, showed that in 60 per cent of the group syphilis had not been previously recognized and treated. As is the case in all studies of this type, it is pointed out that more evidence than a single positive serologic reaction is necessary to

establish a diagnosis of syphilis. In this connection this author found that in 11 per cent of the cases no diagnosis of syphilis could be made after a careful history, detailed physical examination, spinal fluid study and further blood examination. In another 11 per cent the syphilis had apparently been adequately treated, since no evidence of the disease was found. In 13 per cent the disease had progressed to a point where cerebrospinal, cardiovascular or other complications were demonstrable. In the remaining 65 per cent the disease had been inadequately treated or untreated, and although evidence of the disease persisted, there were no complications. The bulk of these latter groups were latent syphilis, that is, the disease had not yet progressed to serious organic changes. This study as well as others indicates the need for careful diagnostic work up including physical examination, to avoid unnecessary therapy of nonsyphilitics and points to the value of the blood tests as indications toward the diagnosis of syphilis.

THE CEREBROSPINAL FLUID EXAMINATION IN THE DIAGNOSIS OF SYPHILIS

PROGNOSTIC TYPING OF SPINAL FLUIDS

(Adapted from Moore and Hopkins 1933 and O'Leary et al Reprint 62, Ven. Dis. Inf., 1937)

	I (Mild)	II (Moderate)	III (Severe)
Blood Serologic Reaction	Negative or positive	Negative or positive	Almost invariably strongly positive
CSF Quantitative Wassermann	Negative 0.2 cc. to 1.0 cc.	Negative 0.2 cc., positive 1.0 cc.	Strongly positive 0.2 cc. to 1.0 cc.
Cells	5 to 25	25 to 100	7 to 100 plus*
Protein	1 plus	2 plus	3 plus
Colloidal Test†	1110000000 0000011000	00244543100	5555543100
Prognosis	Clears with standard or routine treatment for the disease.	Requires 1 to 2 yrs additional standard plus intra spinal or fever.‡	Will not clear with out fever or try parsamide or both.‡

Ten to 20 large lymphocytes and polymorphonuclears may be present.

† Colloidal mastic or gold preferably the former

‡ Recent studies indicating the effectiveness of penicillin in the treatment of neurosyphilis will undoubtedly alter the recommendations as to the type of therapy to be employed but not necessarily the prognostic import of the spinal fluid findings as here tabulated

In recent years the value of the cerebrospinal fluid examination as a guide to treatment and prognosis has been repeatedly emphasized. It is now known that the cerebrospinal fluid may show abnormalities long before the first appearance of symptoms and signs of neurosyphilis. Also, on occasion, the patient may have active neurosyphilis with normal spinal fluid findings. In following the effects of the newer types of treatment such as penicillin and fever therapy, repeated complete examination of the cerebrospinal fluid is indispensable. For the purposes of syphilology a complete examination consists of cell count, protein estimation, Wassermann test, and colloidal test. Although, as Lange²⁸ has pointed out, quantitatively standardized methods are most desirable, in practice these are not always available. Utilizing the currently used tests, the cerebrospinal fluid may be of great prognostic value. The Cooperative Clinical Group has re-emphasized the value of Moore and Hopkins' prognostic grading or typing of cerebrospinal fluid formulas. Although there are some objections to this classification and although active neurosyphilis may rarely exist in the presence of a completely normal cerebrospinal fluid and negative reactions on the blood, the typing is worthy of reproduction for clinical practice.

SUMMARY AND CONCLUSIONS

1 In the past twenty-five years there has been a greater understanding and wider application of the various procedures used in the diagnosis of syphilis.

2 The darkfield examination is, in expert hands, a highly efficient and reliable means of diagnosing syphilis in its earliest phases. Technical modifications such as lymph node puncture, technic for the examination of pus, and the deferred darkfield greatly enhance the availability and practicality of the darkfield procedure.

3 Methods for staining *Spirochaeta pallida* are of little value.

4 The electron microscopic studies of *Spirochaeta pallida* are still of academic interest.

5 The blood tests are valuable means in diagnosis of syphilis. Various modifications in testing, such as the quantitative procedures, yield information of great value to the clinician. The occurrence of biologic false positive reactions does not vitiate the value of the tests in practice. Serologic performance in recent years is becoming more or less standardized. Mass testing is a valuable means of case-finding, but the need for clinical examination for actual definitive diagnosis is stressed.

6 The cerebrospinal fluid examination is an indispensable part of the investigation and treatment of patients with syphilis. By a classification of the findings cited, the prognosis of the case may be anticipated and appropriate treatment instituted.

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TESTS OF HEMOSTATIC FUNCTION IN PATIENTS WITH ABNORMAL BLEEDING

Application and Interpretation

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PRACTICING physicians or surgeons are not uncommonly confronted with one of the following problems

1. A patient is to undergo an elective or emergency operation, and upon being told of the plans says that he fears the outcome, because "he bleeds easily" or is a "bleeder"

2. A patient comes or is brought to the physician because of abnormal bleeding, either into the tissues or from one of the body orifices or cavities.

3. A patient develops abnormal bleeding during the course of an operation or of an acute or chronic illness

How can a tendency to bleed be detected? How can its severity be estimated? How can the nature of the defect be clarified? These are some of the questions that are asked at such times and which I shall try to answer here.

An estimate of the adequacy of a patient's hemostatic mechanism cannot be based solely on the results of the so-called "laboratory tests" for bleeding. Consideration must also be given to what has been learned from the patient himself—especially the answers to certain pertinent questions—and to what was found on physical examination. The evidence must then be taken and appraised as a whole. The error must not be made of considering any of the tests final, since they may be negative in patients who are potential bleeders or yield anomalous results in those with little inclination to bleed.

Abnormal bleeding should be considered moreover, not simply as a manifestation of a "blood dyscrasia" but as the expression of a disorganized function which owes its disorganization more often to acute transitory changes than—as it is generally supposed—to chronic or congenital defects. One is then less likely to make the mistake of thinking of these disorders as something apart from the common clinical entities

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STEPS IN THE STUDY OF PATIENTS WITH ABNORMAL BLEEDING

The History—When questioning the patient regarding his alleged tendency to bleed, less attention should be paid to his statement that he bleeds easily—a not uncommon claim—and more to his answers to certain specific questions, namely, the outcome of previous operations, tooth extractions, traumatic accidents, the need for blood transfusions, the duration and degree of menstruation, and any family history of bleeding.

Patients who have bled excessively at previous operations, especially minor ones such as tooth extractions, are likely to do it again unless properly prepared. If their wounds heal slowly, they are prone to develop delayed hemorrhage which itself retards the healing of wounds and provokes subsequent hemorrhage. If they have required blood transfusions or have been treated for anemia, excessive blood loss must be considered, and the claim that they are “bleeders” must be taken more seriously.

Too much significance must not be assigned to a negative history of bleeding. Like all negative information, it usually has little positive value. If the patient is an infant or young child, it has obviously not lived long enough to develop the complications of any defect it may harbor. Older persons are sometimes indifferent to their own body functions, do not remember past events or deliberately hide or underplay their complaints. Finally, the hemorrhagic disorder might be a recent development, because of a change in the patient himself or in his living conditions.

The Physical Examination—Search is made for ecchymoses (especially when nontender, and in the skin overlying bones near the surface), petechiae about the ankles, suffusions of blood in the oral mucosa (at the mastication line especially), and blood crusts about the nares, lips, gums and the posterior pharyngeal wall. Hemorrhages about incisions, scratch marks or needle punctures are telltale evidence. Telangiectodes, varicosities and prominent superficial veins have some significance. Swellings and partial ankylosis of joints may mean present or previous hemarthroses. Lymphadenopathies, splenomegaly and hepatomegaly suggest disorders like leukemia, cirrhosis of the liver and Banti's syndrome, all of which may be accompanied by abnormal bleeding.

Tests of Hemostatic Function—Upon completion of the history and physical examination the functional tests are made, bearing these points in mind. If the evidence so far has been trivial or insignificant, the tests are made with the hope of uncovering something which has not been disclosed in the preliminary examinations. If the results of the tests fall within normal limits, the assumption is permissible that the existence of a tendency to bleed is unlikely. If, however, there is convincing clinical evidence that the patient *has* a tend-

ency to bleed, the tests are done not so much to confirm the fact as to seek an indication of the nature and severity of the defect. If the tests yield normal results, little has been learned about the problem and certainly the presence of a defect has not been excluded, none simply has been demonstrated. In any case the patient must be regarded as a potential bleeder. He or his physician may be assured that, although not located, a defect undoubtedly exists that it is probably not severe, but that general measures should be taken to combat blood loss and avoid excessive trauma if an operation is contemplated. Under the circumstances more specific information cannot be given but the tests should be repeated, preferably when the patient is bleeding, as during an attack of epistaxis, menorrhagia or melena, when the likelihood of finding the defect is greatest. Even with the best technique, it is not always possible to demonstrate a defect or understand its significance when one is found. This is because we do not fully understand the functional implications of the tests now available, and do not have tests available for certain functions which we know exist.

Tests for hemostatic function may be conveniently divided into two groups

1. *Tests in Vivo*—These involve the application of a stress to the body and comparison of its response with normal standards. Though the stresses rarely equal in magnitude the major stresses incurred by most individuals, if the results are abnormal one may conclude, within the limitations stated above, that should larger stresses be incurred excessive bleeding will result. If however, the results are within normal limits, it does not necessarily mean that excessive bleeding would not occur should similar stresses be applied on areas of the body other than those examined. Moreover, *in vivo* tests simply disclose or confirm the existence of a defect in hemostasis and give an approximate idea of its severity. Without further study, only an inferential guess as to the nature of the defect may be made.

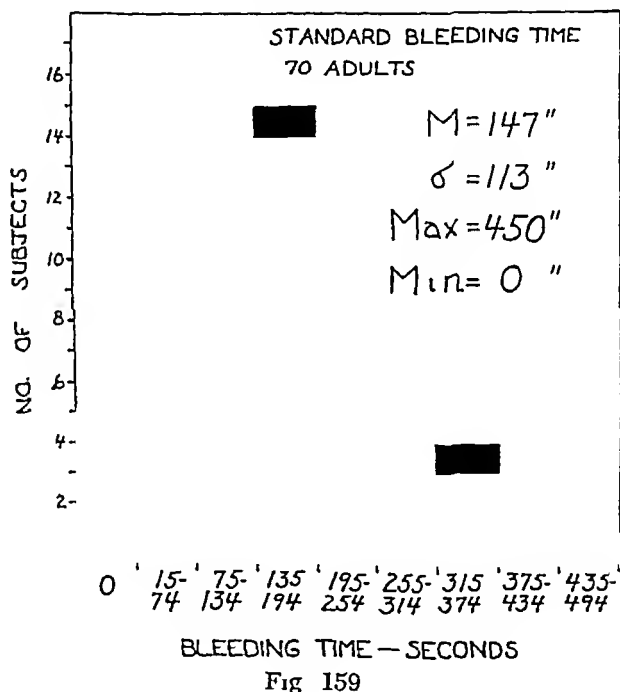
2. *Analytical Tests of Normal Hemostasis*—Hemostasis results from the interplay of a series of factors which for the sake of convenience have been classified as extravascular, vascular and intravascular. With these tests an attempt is made to trace the nature of any existing defect by assessing the efficacy of each one of these factors. An ideal study should cover all factors. Unfortunately those pertaining to the vessels (thickness, contractility, elasticity of the vessel wall) or to the surrounding tissue (tension, elasticity, rigidity of extravascular tissues) are not as yet amenable to quantitative study. Nevertheless, their importance in normal hemostasis must not be underestimated.

IN VIVO TESTS OF HEMOSTATIC FUNCTION

The bleeding time and petechial reaction of the skin are tests involving the application of a stress on a patient and noting his response

to it. They differ from other tests in that they are done *in vivo* and represent in a sense the reaction of the patient's own tissues to a standard form of trauma.

The Bleeding Time of the Skin.—The arrest of bleeding from a cut of the skin is probably influenced by all the factors concerned in spontaneous hemostasis. It is clear, therefore, that a prolongation of the bleeding time could have no specific meaning beyond disclosing the fact or confirming the impression that a defective hemostasis exists. In Figure 159 is shown the range of variation in the values for the bleeding time of the skin in normal persons. It is seen that 95 per cent of normal people have bleeding times from 0 to 373 seconds.



When the stresses are magnified as by maintaining the venous pressure in the forearm at a high level just before the cut, and during the bleeding (the "venostasis bleeding time"), longer times are obtained. Ninety-five per cent of normal persons have venostasis bleeding times from 0 to 536 seconds (Fig 160). Mild prolongations may be taken to represent slight defects, while longer times, especially when the output of blood from the cut shows no signs of tapering off, may be taken to represent a severe defect. Two points, however, must be kept in mind, namely, the variability of the bleeding time in different portions of the body, and its changes in the same area from day to day. It is easy to understand that a vascular or extravascular factor

which would operate in a certain portion of the body and lead to prolongation of the bleeding time there, might not do so in another area. Such variations have forced some observers to resort (principally for research purposes) to the mean bleeding time, a figure representing the results of at least five determinations in different portions of the body. In ordinary clinical work such precautions are perhaps unnecessary and, usually not feasible. The fact that they *are* necessary for accuracy will help in placing a single bleeding time determination in its proper perspective. The other point concerns the variation in the bleeding time in the same area, from day to day. Because of this variability, slight or moderate prolongations are inconsequential

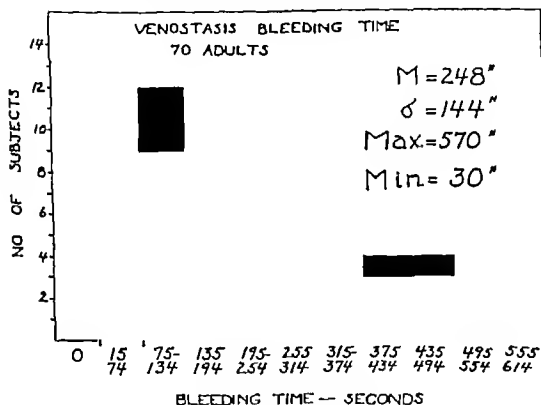


Fig. 160

if when repeated normal results are obtained and no history of bleeding or evidence of defects in other hemostatic factors are present

Even in normal persons the scatter of values is wide (Fig. 161). The patient with a persistently prolonged bleeding time, however even though without a defect in other hemostatic factors should be considered a potential bleeder. It is not easy to estimate on this basis alone how much difficulty there may be with the arrest of hemorrhage, but it should be accepted as a likely occurrence and preparations made for any possible complications resulting from it. A patient may bleed long from the skin however, and yet not bleed significantly from other tissues, and vice versa. This is particularly true when the bleeding is in an area where there is much devitalized, necrotic or infected

with obviously deficient hemostatic function. Conditions prevailing in such areas are hardly comparable to those in the normal skin.

Petechial Reaction of the Skin—There are many methods for testing this reaction, but they are nearly all based on the response of the skin vessels to one of two procedures. In one, the stresses on the vessels are increased from within. The venous pressure in the forearm is raised by constricting the arm with the band of a sphygmomanometer, the pressure within which has been adjusted at a fixed level (usually

Bleeding Time—Normal Men

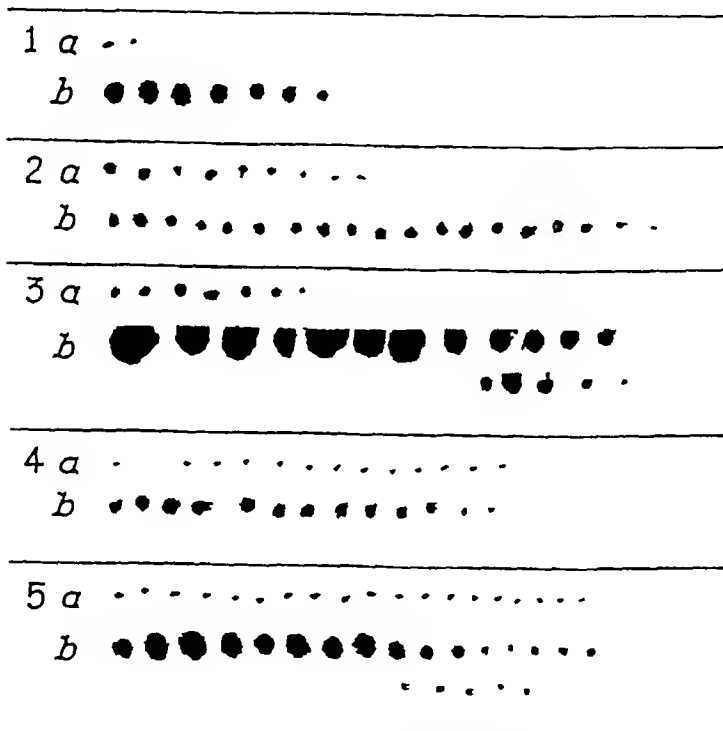


Fig 161—Five normal subjects *a*, Standard bleeding time *b*, Venostasis bleeding time. Each spot represents the blood blotted from the wound at 15 second intervals.

50 mm of mercury) At the end of a given period of time, petechiae are searched for in a previously circled area of the skin. The other procedure consists in exerting the stresses on the vessels from without. Negative pressure is applied with a suction cup to a restricted area of the skin, usually of the forearm, for a fixed period of time, and the number of petechiae appearing within it are counted.

The working conditions for these tests have not yet been well standardized, so that it is difficult to interpret a given result with any

degree of assurance especially when the response is not striking. Normally the resistance of capillaries to internal or external trauma is greater in the skin of the lower extremities than in the upper, and greater in the lower than in the upper portion of the body. It is higher in infants and young children than in adults. Trauma (including the tests themselves) to a section of the skin will alter its reaction for a period of at least two weeks. The temperature of the environment has a significant effect. The vasoconstricting and blood flow retarding effects of cold may reduce the intensity of the reaction considerably.

If the response is striking and numerous petechiae appear in the skin a hemostatic defect undoubtedly exists. Since the mechanism underlying the production of the petechiae, or rather that which should prevent their appearance, is not completely understood, the actual defect cannot often be traced. With the exception of ascorbic acid and the blood platelets, there are no other substances which are *definitely* known to influence capillary fragility. We know that the test is often markedly positive when there is a thrombopenia or C avitaminosis or when there is "capillary disease" due to or accompanying certain conditions (hypertensive disease, chronic nephritis, chronic rheumatic heart disease, anaphylactoid or Henoch's purpura).

A negative petechial reaction, like most negative findings gives little information, and is even of small value in excluding some of the conditions just mentioned. It is not uncommon, especially in the anaphylactoid purpuras, to obtain a negative reaction, although the skin throughout the body is covered with petechiae. The existing hemorrhages arose probably hours or days before the test was performed, at a time when the condition of the vessels was favorable to their development.

When the bleeding time is prolonged, a positive petechial reaction of the skin is often found. There may however be a severe hemorrhagic response in the skin with little or no prolongation of the bleeding time. This is usually the case in the anaphylactoid purpuras and in scurvy.

ANALYTICAL TESTS OF HEMOSTATIC FUNCTION

Let us now turn our attention to those tests designed to supply us with information regarding the intravascular factors. Much of our knowledge of these factors has come from study of the blood.

The Coagulation Time of Venous Blood—Venous blood is generally employed because studies of coagulation of cutaneous blood ("capillary clotting time") are often misleading. The coagulability of blood should be measured in samples of adequate volume, obtained directly from a vein, after a quick puncture, with little or no admixture of tissue juices. Under certain circumstances, to be described later, valuable information can be obtained from the study of *cutaneous* blood.

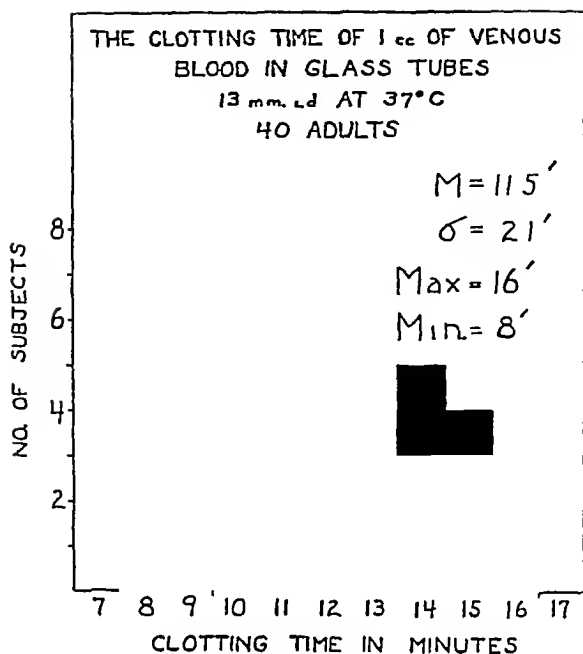


Fig 162

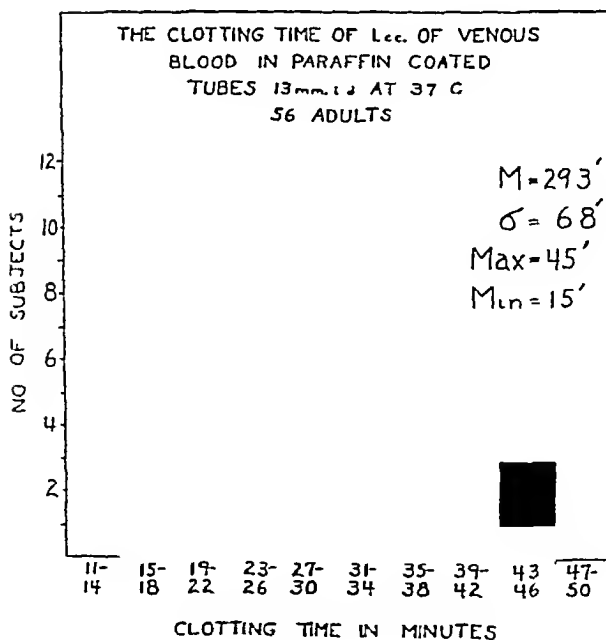


Fig 163

When the coagulation rate is measured in glass tubes at 37°C, the mean normal value is 11.5 minutes and variations as shown in Figure 162 may be expected. In any one person, a *single* reading cannot be considered abnormal, unless it falls outside of the limits of twice the standard deviation on either side of the mean. Thus if a reading of less than 7 minutes is obtained the blood may be considered hypercoagulable. If it is longer than 15 minutes it is hypocoagulable. Paraffin or similar surfaces lend themselves to the detection of slight changes in rate, because the stability of blood is better maintained in contact with paraffin than with glass. In paraffin coated tubes the blood of ninety five per cent of normal persons takes between 15 and 42 minutes (Fig 163) to clot. Certain bloods may be only slightly hypocoagulable when tested in glass tubes and yet display pronounced hypocoagulability when tested in plastic or paraffin coated surfaces. Occasionally a patient with mild hemophilia may be discovered in this way.

We cannot at this time go into an extended consideration of the mechanism of blood coagulation. A few facts may help in understanding better what is to follow. Circulating blood contains within and about itself all that is necessary to delay or promote coagulation. Two opposing groups of factors affect the appearance and rate of development of coagulation.

Anticoagulant (Agents preventing or retarding coagulation)	Coagulant (Agents promoting or accelerating coagulation)
1. Intact vascular endothelium.	1. Damaged or altered vascular endothelium.
2. Anticephalin (or antithromboplastin)	2. Cephalin (platelets, leukocytes, tissue juices)
3. Antithrombin.	3. Prothrombin
4. Fibrinolysin.	4. Fibrinogen.

A delayed rate of blood coagulation may be the result of an uncompensated increase in the anticoagulants of the blood or a decrease in the coagulants. When the reverse happens, clotting is accelerated. An excess of anticephalin activity is manifested by a slow response of the blood to the addition of clot accelerating cephalin suspensions, especially when the test is carried out in paraffin or collodion coated tubes. It is the characteristic defect of hemophilic blood. The defect may be detected even in cutaneous blood, provided the first few drops are used and the blood is flowing freely. Excesses of antithrombin activity are rarely encountered clinically except, of course, in patients receiving anticoagulants, such as heparin, therapeutically. Excesses of fibrinolysin activity are likewise seldom seen. The patient's blood may be hypocoagulable because of an uncompensated diminution in the coagulant factors, namely prothrombin,

fibrinogen, platelets (cephalin) Perhaps the commonest cause for hypocoagulability is a diminution in plasma prothrombin

Prothrombin—Hypoprothrombinemia and thrombopenia are probably the most frequent defects *in the blood* that interfere with the proper arrest of bleeding It is fortunate that we now have fairly dependable methods for measuring blood prothrombin The most practical and informative of the methods, in my estimation, is the bedside method It does not require much equipment, except for a potent thromboplastin solution, which is now made available by several commercial houses The time required to produce clotting when this solution is added to 1 cc of blood from normal subjects is taken as a standard The principal difficulty which existed originally, that is, of securing fairly stable preparations of thromboplastin, of uniform potency, has apparently been overcome Prothrombin determinations done on plasma by the Quick method, take longer to perform and require more equipment, but they are likewise helpful Neither one of these methods will, however, furnish occasionally desired information, especially in a controversial case, namely, just how many units of prothrombin exist in a given amount of unknown plasma? This information can be provided only by a more elaborate method, carried out in two stages, with the results expressed in number of units of thrombin formed

Clinical exigencies seldom require greater accuracy in the prothrombin determination than is supplied by the one-stage method If the patient has less than 25 per cent of normal of prothrombin this fact may be assumed to have some relation to his tendency to bleed Again, the low finding may be only temporary and require confirmation If there is hypoprothrombinemia even after vitamin K has been administered, the probabilities are that it bears some relation to the patient's disorder It must be borne in mind, however, that hypoprothrombinemia may exist without a tendency to bleed and without even a delay in the rate of blood coagulation

One must avoid the error of considering the level of the plasma prothrombin as the *dominant* factor in determining the rate of coagulation A good example of the fallacy of this belief is the oft encountered hypercoagulability of the blood after acute hemorrhage, when the prothrombin is usually diminished This is because, even though the amount of prothrombin is reduced, its rate of conversion to thrombin is accelerated This accelerated prothrombin conversion rate (due to a diminution in anticephalin activity) causes thrombin to be formed faster than normal Now, less than one-fourth of all the prothrombin available in *normal* blood is changed into thrombin before solid clotting occurs It is apparent, therefore, that even if the prothrombin in the blood is, say 25 per cent of normal, if that amount is changed *rapidly* into thrombin, the blood will clot quicker than

when the thrombin is made slowly, though there may, eventually, be more of it available. Thus no single factor alone determines what the rate of coagulation shall be. Rather, each factor is constantly influencing and conditioning the performance of the others.

Fibrinogen.—Hypocoagulable and incoagulable blood may also result from a scarcity or absence of fibrinogen. Fibrinogenopenia has been noted in advanced hepatic failure and in certain persons, as a congenital defect. No coagulation can take place without fibrinogen. Normally, there is an excess of this protein in the blood (Table 1).

TABLE 1 —PLASMA FIBRINOGEN LEVELS IN NORMAL SUBJECTS

Reference	Fibrinogen (mg./100 ml plasma)		Number of Subjects	Ages (yr)	Number of Determina tions
	Mean	Range			
Gram, H. C., J. Biol. Chem., 49 279 1921	270	200-360	25 males	16-19	25
	290	210-380	25 females	20-52	25
Starlinger W and Winanda, E., Zt. f. Ges. Exper Med., 60 138 1928	250	220-360	1 male 15 females	20-32	25
Gilligan, D. R., and Ernste, A. C., Am. J. M. Sc., 187 552, 1934	250	200-310	25 males 12 females	15-35	43
Ham T. H., and Curtis F., Medicine, 17 413 1938	250	190-330	19 males	25-61	54
	250	220-290	9 females	20-35	21

Adapted from Ham, T. H. and Curtis F. Medicine, 17 413 1938.

Low amounts of fibrinogen do not significantly alter the rate of coagulation of blood, but do obviously influence the physical properties of the clot.

Diminutions in the amount of fibrinogen have rarely by themselves accounted for defective hemostasis. There have been reports of excessive bleeding in patients who had in the blood 50 mg or less of fibrinogen per 100 cc. In an even smaller number of persons, no fibrinogen whatsoever has been found—apparently a congenital defect. This anomaly is so rare that most practitioners never encounter it. It

be considered when the hypocoagulability or incoagulability cannot be explained on other grounds. More commonly, when there is fibrinogenopenia, the prothrombin is also reduced. Patients with both defects are poor operative risks, unless properly prepared.

The Blood Platelets.—No study of hemostatic function is complete without an accurate count of the platelets. The platelets are intimately connected with formation of the "hemostatic plug" and are particularly useful in injuries of the capillaries and small blood vessels. Hemostasis at the level of these vessels is probably due to the combined action of

TABLE 2 —NUMBER OF PLATELETS IN *VENOUS* BLOOD, ACCORDING TO VARIOUS AUTHORS

Author	Number of Platelets (thous/cu mm)		Number of Subjects	Remarks
	Mean	Range		
Kristenson, A, Uppsala Thesis, 1924	294	204-395	138 males under 60 years old	Direct method
	291	214-360	20 females under 60 years old	
Tocantins, L M., Medicine, 17 155, 1938	310	88-532 ($2 \times S D$)	40 men	Direct method
Aynaud, M, C R Soc Biol, 68 1062, 1910	216	183-252	8	Indirect method
Preiss, W., Zeit Ges Exper Med., 84 810, 1932	350	320-450		Indirect method

S D—Standard deviation

platelets, vascular collapse or contraction, and compression of the injured vessel by the surrounding tissue. Then platelets also help to initiate and accelerate the coagulation of blood, and to lend rigidity and strength to the framework of the clot. We cannot measure all of these changes, but we can estimate the number of platelets in the blood. The platelets are most easily counted (in experienced hands) in cutaneous blood by the direct method. If the results are questionable and if close accuracy is desired, venous blood should be used, collecting it directly into the anticoagulant (Table 2). In any event, and

especially when a low platelet count is reported, the findings should be verified by a careful inspection of a well made, well stained blood smear. The edges and the area at the beginning of a smear, where the platelets are most likely to have gathered, should be given particular attention, noting the number, size and staining characteristics of the platelets. A rough estimate of the proportion of platelets to red blood cells, which normally is about 1 to 20, is made. If such proportions are found in the smear the accuracy of a low platelet count is in question and the count should be repeated with added precautions.

The patient may have a low platelet count and yet have no signs of bleeding, but anyone with a platelet count under 75,000 should be considered as a potential bleeder and preparations made for any eventuality, if an extensive operation is contemplated. Such patients may, however, experience little trouble with minor operations not entailing much destruction of tissue. The thrombopenia of the patient may moreover, be temporary, when the count is repeated a few days later it may be normal. If the patient has had no signs of bleeding and has a negative history too great stress need not be laid on the thrombopenia.

If there has been excessive bleeding but the platelet count is normal it does not follow that the platelets are not connected with the bleeding disorder. The chances are that the bleeding is due to other causes nevertheless the relatively rare disorder called thrombasthenia should be considered. In this disease, nearly always congenital the platelets are in normal number but they do not clump as they should after the blood is shed, and apparently do not adhere to walls of injured blood vessels and form the necessary hemostatic plug. Since they are ineffective functionally, the functions for which they are responsible remain undone. The end result is the same as if a thrombopenia existed. The patient with thrombasthenia presents a clinical picture indistinguishable from that of thrombopenia, with which it is often confused, sometimes (as when splenectomy is undertaken) with regrettable results.

With every platelet count, the bleeding time of the skin should be determined. The patient may bleed from a small cut for a long time even though his platelet count is normal since other causes may be operating. When the number of platelets is reduced below 50,000, the bleeding time when properly determined is nearly always prolonged. It has been said that the only way of determining whether a person will actually bleed longer than he should, is to cut his skin and time the resultant bleeding. This is obviously true. What is often forgotten is that the skin should be cut and not simply punctured that the cut should be moderately deep (3 to 4 mm) and in an area where the skin is not excessively thick.

Clot Retraction—After the blood has clotted, retraction should be

looked for In Figure 164 are given the variations in the degree of clot retraction in normal persons It may be seen that the clots of 95 per cent of normal people express between 61.9 and 94.3 per cent of the serum contained within the clot Retraction of the clot is chiefly dependent on the quality of the fibrin and the presence of an adequate number of normal platelets If the clot from the patient's blood retracts poorly or not at all at 37°C, within two hours after it is formed, one or more defects are probably present Absence of clot retraction is not indicative of any particular disorder, but it does help

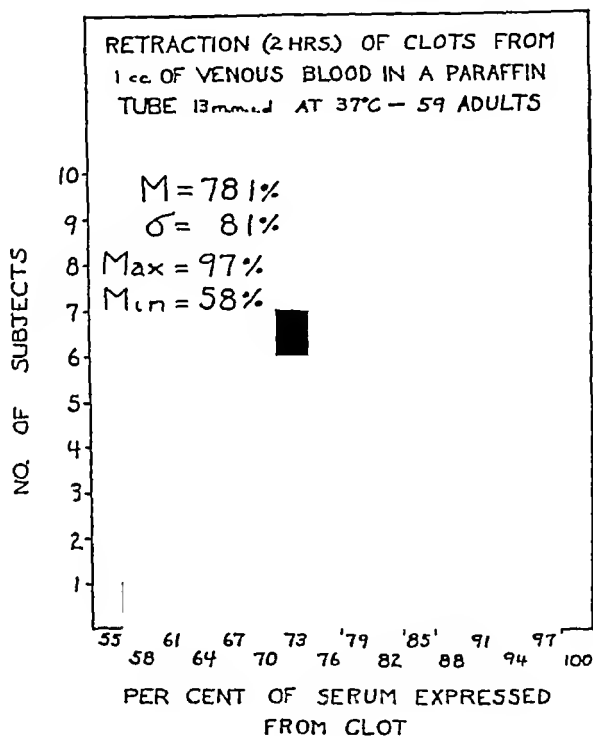


Fig 164

to confirm the impression that the defective hemostasis originates probably in the blood and is related to the fibrin or platelets Clots may not retract when the amount of fibrin deposited is small, because of a deficiency in thrombin They will likewise retract slowly or not at all, if the number of platelets is under 50,000 per cu mm, or if the platelets are of the type which will not clump, even though they are present in normal numbers Thus, when the blood of a patient clots within the normal time but does not retract, the existence of any one of the above possibilities may be suspected or confirmed

Calcium - Calcium is known to play a part in blood coagulation

but its clinical significance has been greatly exaggerated. As far as we know, there is no disorder of bleeding that is due to a deficiency or excess of blood calcium. Likewise, no adequate demonstration has been given that calcium compounds have any therapeutic value in these disorders.

If a patient has *hypercoagulable* blood it is reasonable to suppose that he has an uncompensated diminution in the substances required for the retardation of coagulation (anticephalin, antithrombin) or an increase in those that promote the process. In any event, too much concern need not be felt regarding his liability to bleed, since hypercoagulability of the blood would tend to counter that tendency. Incidentally, the hypercoagulability may represent the reaction to a recent hemorrhage. Moreover the patient's blood may be hypocoagulable without his incurring any bleeding or, in turn, the blood may be hypercoagulable without signs of thromboembolism. The tendency should be sharply differentiated from the actual existence of these manifestations. They may never eventuate unless favorable circumstances (trauma, infection, stasis) intervene, while the abnormal changes in the blood are maintained.

LYMPHADENOPATHY

A Clinicopathologic Study

FRANK W KONZELMANN, M D , F A S C P * AND
CHARLES HYMAN, M D †

CLINICAL PRESENTATION

DR HYMAN The first patient to be presented is a Negro woman (Mis M B), aged 21 years Her chief complaint is bilateral enlargement of the sublingual lymph nodes of nineteen years' duration After an attack of mumps at the age of two these glands began to enlarge The increase in size occurred slowly until the age of 15, when there was a noticeable increase in the rate of growth The birth of a baby three years ago also seemed to have an effect on the rate of growth One year ago her physician noted on examination a rash about the thighs and vulva which gave rise to the complaint of itching The rash and itching soon subsided At this time she was suffering from an attack of "sore throat" and the sublingual masses seemed to have become larger and somewhat painful and tender There was also enlargement of the anterior cervical nodes which, too, were tender Cervical and sublingual nodes would swell and become tender whenever she had a "cold" The acute swelling would subside after recovery from the "cold," leaving the masses just a little larger than they were prior to the acute infection There was no enlargement of the spleen or axillary nodes An indefinite mass was palpable in the lower abdomen It seemed to be an elongated mass at about the level of the anterior superior spines of the ileum It was not tender There had been a moderate weight loss of several pounds In May of 1945 the mass in the left thigh was removed for microscopic study

Physical examination of this patient reveals a slender but not poorly nourished young Negro woman There is a slight reddening of the pharyngeal mucosa, the anterior cervical nodes on both sides vary from 1 to 3 cm in diameter The right epitrochlear node is just palpable The right sublingual nodes form a mass about 6 by 3 cm , one node is about 3 cm in diameter They are discrete, the overlying skin

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is not involved nor adherent. On the left side there is a much thickened scar the site of surgical removal of nodes. Beneath it several nodes, 1 to 3 cm. in diameter, are palpable. These nodes are not tender at the present time. The spleen is not palpable. The indefinite mass previously described is still present. Examination of the heart, lungs and pelvic organs reveals nothing noteworthy. Laboratory findings show the blood Wassermann to be negative. The tuberculin test is negative. The blood counts are as follows:

	4/11/45	4/19/45	2/1/46	7/30/46
Erythrocytes	4 77		4 11	3 78
Hemoglobin	11 gm		13 gm	11 gm
Mean corpuscular hemoglobin			31	29
Leukocytes	6 750	7 100	9 950	8 950
Differential Count				
Filament neutrophils	64	59		32
Nonfilament neutrophils	9	29		28
Eosinophils	0	0		8
Basophils	0	1		0
Lymphocytes	24	8		23
Monocytes	1	0		9
Blast forms	2	8		0

X ray examination of the skull, long bones and the gastrointestinal tract on May 23, 1945, as reported by Dr. Charles B. Kaign, was negative. The lungs showed only increased hilar shadows.

The biopsy performed on May 5, 1945, will be described later.

The findings in this case, exclusive of the biopsy, lead me to consider the following conditions in the diagnosis:

1. Chronic lymphadenitis
2. Tuberculosis
3. Mycosis fungoides
4. Benign lymphoma with possible beginning malignant change

The second patient is a white woman, aged 21, whose chief complaint was enlargement of the right supraclavicular nodes. Increase in size developed rather suddenly. The mass measured about 5 cm. in diameter. It was not painful or tender. The patient states that it became so after repeated palpation. Two weeks previously she had had a fever, sore throat and headache. After one week a small dose of x ray was administered. Headache became progressively worse, fever rose to 103° F., then over a period of about ten days the symptoms subsided except that the node remained large and became very firm. It was not tender or painful at this time nor was there any redness of the overlying skin. The skin seemed slightly adherent to it. There has been no weight loss.

Physical examination reveals a well nourished, young, white woman. There is a slight reddening of the pharyngeal mucosa. The superficial

vessels are injected. The tonsils are deeply embedded and atrophic. The anterior cervical nodes are bilaterally slightly enlarged. There is a recent scar, the site of surgical removal of the supraclavicular node on the right side. There are no other palpable nodes. The spleen is not enlarged. Examination of the heart, lungs and abdomen reveals nothing noteworthy.

The laboratory reports the blood Wassermann to be negative. The blood counts are as follows:

	Sept, 1945	11/10/45	11/20/45	11/26/45	1/17/46
Erythrocytes	4 19		3 97		4 76
Hemoglobin	11.5 gm		11.5 gm		12.5 gm
Mean corpuscular hemoglobin	29		29		26
Leukocytes	6,600	7,000	6,600	7,900	5,500
Differential Count					
Filament neutrophils	38	32	9	37	24
Nonfilament neutrophils	23	20	50	23	42
Lymphocytes	35	36	32	31	20
Monocytes	2	6	6	6	14
Eosinophils	2	4	2	3	0
Basophils	0	2	1	0	0
Abnormal cells	0	0	0	100% lympho- cytes deeply basophilic	0

Heterophile antibody reaction

- 11/15/45 Positive in dilution of 1:112. Davidsolin differential absorption test not typical of infectious mononucleosis.
- 11/24/45 Positive to dilution of 1:448. Differential absorption test not typical of infectious mononucleosis.

The findings in this case exclusive of biopsy lead me to consider the following conditions in the diagnosis:

1. Acute lymphadenitis
2. Infectious mononucleosis
3. Lymphatic leukemia
4. Hodgkin's disease
5. Metastatic tumor

CLINICAL PATHOLOGY

DR KONZELMANN: These two difficult cases present diagnostic problems, the first because of its long duration, the second, because of its rapid development and confusion of clinical and laboratory findings.

Let us consider some of the *causes of lymph node enlargement* They may be classified as follows

INFLAMMATORY GROUP

Acute Lymphadenitis

Associated with acute infections In addition to the lymphadenopathy of infected wounds and mucous membranes one must consider the involvement of the regional nodes in bubonic plague, tularemia, lymphopathia venereum and generalized lymphadenopathy in trypanosomiasis, kala azar brucellosis, and leptospirosis

Chronic Lymphadenosis

Associated with degenerative or hemorrhagic lesions in areas drained Characterized by proliferation of reticulum cells Associated with chronic infections (non-specific)

Chronic Lymphadenitis

Infectious Mononucleosis

A disease of young adults with characteristic symptoms and blood picture. Heterophile antibody reaction using the Davidsohn differential absorption test helpful.

Infectious Lymphocytosis

A disease of children, characterized by high lymphocyte counts Lymph nodes are slightly enlarged or not at all. Biopsies show chiefly hyperplasia of retothelial elements Lymphocytes in the bone marrow

INFECTIOUS GRANULOMAS

Tuberculosis

Tuberculous cervical lymphadenitis not so common as previously Diagnosis often by biopsy alone, unless node is caseating and a sinus develops

Syphilis

Chiefly in the primary and secondary stage when clinical evidences are usually present.

Boeck's Sarcoid

Occurs in adults, children rarely Affects skin, lymph nodes lungs and bones chiefly X ray examination of lung often diagnostic. Increase in serum globulin. Microscopy usually diagnostic.

Hodgkin's Disease

A disease of young and middle-aged adults Clinical findings or x-rays may be diagnostic. Biopsy usually diagnostic. Blood picture not helpful

Disseminated Lupus Erythematosus

Clinical findings usually diagnostic. Butterfly pattern of eruption on the cheeks and nose, fever leukopenia Biopsy usually helpful

Mycosis Fungoides

Lymph nodes may be involved but skin lesions are usually diagnostic. May occur in late stages of leukemia or Hodgkin's disease Biopsy diagnostic.

METABOLIC DISORDERS

Lipodystrophy

A condition affecting mesenteric nodes, collections of fat and fatty acids occur in the lymph sinuses Biopsy diagnostic Condition is rare

Gaucher's Disease

Lipoid histiocytosis involving reticulo-endothelial tissue Disease is familial, begins in infancy or childhood, and may have a prolonged course Deposits of kersin are found in liver, spleen, lymph nodes and bone marrow Clinical picture characteristic Biopsy and microchemical studies of nodes diagnostic Flask deformity of femur by x-rays

Xanthomatosis and
Hand-Schuller-Christian Disease

Clinical signs and symptoms usually characteristic X-ray findings in skull of latter helpful

NEOPLASMS (Diagnosis by biopsy)

Lymphadenoma

A benign lesion, may remain benign for years May become malignant

Giant-follicle Lymphosarcoma

A slow-growing tumor of middle age, may undergo spontaneous regression Patient may die of intercurrent infection Tumor may take on rapid growth and metastasize

Lymphosarcoma
Reticulum Cell Sarcoma
Lymphatic Leukemia

With or without leukemia Rapid growth
With or without leukemia

With or without leukemia Nodes not always enlarged with leukemic blood Acute variety in children and adults Chronic variety in those of advanced years

Metastatic Tumors

Usually affects regional nodes first Sentinel node involvement of left supraclavicular node in carcinoma of stomach

Procedure in Diagnosis—1 *Case History and Physical Examination*—From this list of causes of lymph node enlargement—and it is by no means complete—and from the comments made on each condition, it should be apparent that the first step in the study of any case is the recording of a complete history of the patient and his illness, not one limited to questions concerning the enlarged node Such enlargement frequently is only a secondary manifestation of disease elsewhere in the body For the same reasons a careful examination of the patient from head to toe is likewise necessary Frequently a diagnosis can be made from these findings alone Confirmation by a few well chosen laboratory or x-ray studies may then follow with the least expense and discomfort to the patient Immediate reference to the roentgenologist or pathologist is to be condemned, for either of these

must know the history and physical findings before he can apply intelligently the tools of his specialty

2 *The Blood Picture*—The cell count and the stained film will often aid materially in confirming the clinical diagnosis and will add valuable information which may help in making the diagnosis. Red corpuscle fragility and platelet counts may provide valuable information.

3 *Special Studies*—From the information thus far obtained special studies may be indicated, as follows: x ray examination of the chest for lymph node involvement by Hodgkin's disease or lymphosarcoma, Boeck's sarcoid, or primary tumor of the lung, of the gastrointestinal tract for primary neoplasm of the long bones for Hodgkin's disease or Gaucher's disease, of the skull for neoplasm or Hand Schüller Christian disease, special chemical studies of the blood in xanthomatosis of diabetes, and special serologic studies such as the heterophile antibody reaction.

When the *heterophile antibody reaction* is employed the differential test of Davidsohn should be performed on all positive serums. The so-called presumptive or simple test should show a titer of at least 1:224 and there should be clinical signs to support the diagnosis of infectious mononucleosis in a patient who has not received horse serum in recent weeks. A titer of over 1:224 may be considered as positive unless the patient is suffering from serum sickness or has recently had serum sickness. The heterophile antibodies in serum disease are of the Forssman type, while the heterophile antibodies in infectious mononucleosis are not. Davidsohn has shown that these antibodies anti sheep agglutinins, are absorbed by boiled beef red cells from the serum of patients suffering from infectious mononucleosis and with serum disease. Therefore, serum from patients suffering from either of these conditions when treated with boiled beef red blood cells, will not show a positive heterophile antibody reaction, that is to say agglutination of sheep cells after such treatment will not occur. The heterophile antibodies in serum disease are readily absorbed by a suspension of guinea pig kidney, and therefore a serum showing a positive agglutination test for sheep cells in the presence of serum disease will lose the ability to agglutinate sheep cells after the absorption by guinea pig kidney. Davidsohn recommends after finding a positive heterophile antibody reaction, that the serum treated with both boiled beef corpuscles and with guinea pig kidney tissue. In the case of infectious mononucleosis he states, "The guinea pig kidney will effect the partial removal of agglutinins for sheep cells but not less than one fourth will remain." For example: If the titer before absorption was 1:224 after absorption with the guinea pig kidney it should be not less than 1:50. If all or almost all of the agglutinins are removed the condition is probably not infectious mononucleosis.

In infectious mononucleosis the agglutinins are completely or almost completely removed by beef cells

4 *Bone-marrow Aspiration*—Bone-marrow aspiration may yield diagnostic information in leukemia, Gaucher's disease, Hodgkin's disease, Boeck's sarcoid, and malignant tumors

5 *Biopsy*—As a last resort, biopsy is to be considered. It may be necessary when all other procedures have failed or when malignancy is suspected. It is important that the pathologist have all of the facts when studying the tissue

Comment on the Two Cases—*Case I*—The negative tuberculin test does not rule out tuberculosis, for if the lesion has healed the reaction may become negative. Mycosis fungoides seems unlikely for there is no skin lesion. The rash described would hardly cause one to think further of this disease.

Biopsy seems the only procedure which might reveal the character of the lesion. In this case it was not too helpful. The nodes were fused in a rubbery, firm, encapsulated mass, measuring 5 by 4 by 4 cm. The incised surface was light yellow, opaque and lobulated. Microscopically the architecture of lymphoid tissue is recognizable. There are follicles of various size, none are very large, many possess active germinal centers. In the pulp and in some of the sinuses there are large pale cells, possessing round, delicately marked but deeply stained nuclei, which I consider to be retothelial cells. Scattered among them are a few lymphocytes and lymphoblasts. There are also large collections of plasma cells in the pulp. No material is available for fat stain so that some form of xanthomatosis cannot be ruled out until another biopsy permits this further study. The histology is not characteristic of any of the causes listed above except a chronic infectious process.

No infection could be discovered clinically, yet this patient did complain that with every "cold" these masses would swell and become tender, subsiding again when she recovered from her acute infection. Her most recent blood count shows a progressive, normocytic anemia, a moderate left shift of neutrophils and eosinophilia. This picture is suggestive of chronic infection. The weight of evidence is in favor of the diagnosis of *chronic infectious lymphadenitis*. I suggest another biopsy so that the node can be studied bacteriologically and from the standpoint of a metabolic disorder. I believe an attempt should be made to relieve her anemia.

Case II—Infectious mononucleosis seems unlikely when one considers the heterophile antibody reaction after absorption of the patient's serum with beef cells and guinea-pig kidney. The blood picture is not suggestive of, nor does it rule out, leukemia. The symptoms are

not at all characteristic of either Hodgkin's disease or metastatic tumor yet these two conditions cannot be entirely ruled out.

Because of the location of the tumor I would have preferred to delay the biopsy and proceed at once with gastrointestinal x ray. Had the x ray findings been negative I would have waited and watched the blood picture. Other consultants thought differently and therefore biopsy was performed. The mass was so firmly attached to the surrounding structures that the surgeon did not attempt to remove it in its entirety. Two portions were excised each a centimeter in diameter. They each presented a granular yellow homogeneous surface. The tissue was quite firm. Microscopically it resembles somewhat the previous node in that there is marked proliferation of the retrothelial cells. There is also proliferation of the fibrous reticulum of the node. There are scattered eosinophils and occasional small, multinucleated cells containing two three or four nuclei. These are nothing like the Reed Sternberg cells of Hodgkin's disease. The striking feature is numerous large collections of polymorphonuclear leukocytes about a necrotic center this evidently denoting infection as a causal factor. To support this view the blood picture shows a left shift though there is no leukocytosis. The basophilic lymphocytes are suggestive of either a virus or streptococcal infection.

Clinically there is now evidence, six months after the acute episode, of residual infection in the pharynx. The blood count of January still shows evidence of infection. I believe the diagnosis in this case must be considered to be *subacute or chronic suppurative lymphadenitis*.

SUMMARY

DR. HYMAN—The clinical findings in these two cases were not at all characteristic of any disease process. Simple laboratory procedures and x ray studies failed to assist in differential diagnosis.

Biopsy in the first case ruled out many of the known causes of lymph node enlargement but was not sufficiently characteristic to permit an unqualified diagnosis. The patient is being kept under observation and another biopsy will be made for completion of the studies if she gives her consent.

In the second case the biopsy definitely ruled out infectious mononucleosis, lymphatic leukemia, Hodgkin's disease, and metastatic tumor. The patient's subsequent course has further substantiated the diagnosis of an inflammatory lesion.

CANCER CELLS IN BRONCHIAL SECRETIONS

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SINCE the only unequivocal criterion for the diagnosis of carcinoma of the lung is the histologic demonstration of cancerous tissue, the procuring and preparation of suitable material for microscopic study is of paramount importance. Currently, the most popular material is tissue removed directly from the tumor, with the aid of the bronchoscope, by way of aspiration through the chest wall, or by incision into the tumor proper at the time of thoracotomy. In the laboratory the tissue is embedded in paraffin, sectioned with a microtome and studied histologically. While this laboratory procedure is highly efficient, once tissue is obtained, the location of the neoplasm often precludes the securing of an appropriate portion of the tumor early enough in the course of the disease to allow complete removal of the cancer and a cure for the patient. In most of our cases in which tissue could not be obtained with the aid of the bronchoscope we have been able to demonstrate neoplastic cells in bronchial secretions that were removed at the time of the first bronchoscopic examination¹ and thus hastened a positive morphologic diagnosis by weeks and perhaps months. A follow-up of these cases has conclusively demonstrated that the method is as foolproof as any other known pathologic procedure in use today and, therefore, can be highly recommended as another aid in the diagnosis of this highly fatal disease.

Since the only escape of bronchial secretions from the body is by way of the sputum one should be able to identify cancer cells equally well in either material, but this is not the case, for obvious reasons. First, fully half the patients with bronchogenic carcinoma have no expectoration of sputum until the disease has progressed to an incurable stage. In fact, even with the aid of a bronchoscope, we have often failed to obtain enough secretion to make a single smear! Second, when sputum is present it is usually so abundant and so dilute that a search for cancer cells becomes tedious and the results are disappointing. Although our experience with examination of sputum for

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cancer cells has been duplicated by most observers from the other major clinics in the United States, there are many reports, mostly from other countries, to the contrary¹ Some of these observers reported finding cancer cells in the sputum in over 85 per cent of the cases examined, a figure which is hard to reconcile with our own

For this clinic it is our purpose to present (1) a detailed account of the technic which we employ, (2) a description, with illustrations, of the appearance of various cancer cells which we have encountered, and (3) a tabulation of our results to May 1, 1946

TECHNIC

A bronchoscopic examination is performed in the usual manner and the secretions are secured from the area just proximal to the location of the suspected neoplasm These are collected in an ordinary collector, if the amount is copious, or in a special collector attached directly to the aspirator without an intermediate rubber tubing, if the amount is scanty When there is not enough secretion present to permit collection of even a drop, the aspirator may be washed with a drop or two of normal saline—just enough to remove what secretion may be in the lumen—or smears may be made directly from the outer surface of the tip of the aspirator and fixed while still wet We have tried washing with a larger amount of saline and also making smears from material secured with a swab, but neither method has been very satisfactory

The secretions are sent to the laboratory, where smears are made as soon as possible One may wait an hour or two, so long as the material does not dry, but the longer one waits the more poorly will the cells stain If the secretions are scanty, all that is sent to the laboratory is smeared but if they are abundant, they are first poured into a Petri dish placed upon a contrasting background and with applicators those areas containing small sloughed particles or streaks of blood are picked off and transferred to slides Routinely six smears are made, but in equivocal cases we have made as many as twenty four A drop or two of secretion is placed near the top of one slide This is covered with another slide and, with back and forth movement and firm pressure, the secretion is spread uniformly over each slide to a thickness of an ordinary blood smear If pieces of tissue are present they have a tendency to slip peripherally so that one must watch them closely to insure their being crushed and smeared properly The slides are then pulled apart, immediately dropped into a mixture of equal parts of 95 per cent alcohol and ether, where they are allowed to fix for thirty minutes they are then stained by the Papanicolaou technic.² To send slides by mail one need only remove them from the fixative, allow them to dry and ship them unstained. Such slides

kept at room temperature for four weeks, or presumably longer, will take the stain just as well as those stained immediately

The staining technic as devised by Papanicolaou² is used without modification, and for the sake of completeness this technic is outlined here

Stain EA 36 is made up as follows light green SF yellowish 45 cc of 0.5 per cent solution in 95 per cent alcohol, bismarck brown 10 cc of 0.5 per cent solution in 95 per cent alcohol, eosin yellowish 45 cc of 0.5 per cent solution in 95 per cent alcohol, acid phosphotungstic 0.2 gm., and lithium carbonate one drop of saturated aqueous solution. The 0.5 per cent alcoholic solutions are first prepared by heating and the solutions are combined and kept in stock without being filtered. Stain OG 6 is composed of 100 cc of 0.5 per cent solution of orange G in 95 per cent alcohol and 0.025 gm of acid phosphotungstic. The actual staining is carried out as follows (1) Fixed smears are rinsed in 70 per cent and 50 per cent alcohol and distilled water (2) Stain in Harris hematoxylin seven minutes. Rinse in distilled water. Rinse three times in 0.5 aqueous solution of hydrochloric acid. Rinse in water. Differentiate for one minute in a solution of lithium carbonate (3 drops of a saturated aqueous solution per 100 cc water). Rinse thoroughly in water (3) Rinse in distilled water, then in 50 per cent, 70 per cent, 80 per cent and 95 per cent alcohol (4) Stain for one minute in OG 6 (5) Rinse five times in each of two jars containing 95 per cent alcohol to remove excess stain (6) Stain in EA 36 for two minutes (7) Rinse five times in each of three other jars containing 95 per cent alcohol. Rinse in absolute alcohol, clear in xylol for ten minutes and mount in Canada Balsam

The smears are then ready for microscopic examination. Unlike the procedure in tissue work, higher magnification should be used in the study of individual cells, we ordinarily employ a low magnification of 80 to scan the slide and a high of 400 to observe details. Because of the irregular distribution of cancer cells it is very important to examine every portion of every slide.

PATHOLOGY

Gross—As already implied, the amount of secretion varies from none at all to several cubic centimeters. When undiluted with saline, it is almost always rather thick and tenacious so that it adheres closely to the collector. The color varies considerably, but usually there is at least some streaking of red or brown or a diffuse pinkish tinge to indicate the presence of recent or old blood. This, however, is not always present, for occasionally secretions positive for cancer cells are pearly white. Conversely, too, blood streaked secretions are present in other conditions, notably in pulmonary tuberculosis. Several times bits of sloughed cancer tissue measuring as much as 1 mm in diameter have been found. They are almost always pink to gray, they are quite friable and are easily crushed between the slides.

Microscopic.—Because primary carcinomas of the lung are extremely pleomorphic, one is hardly justified in classifying them too

rigidly Nevertheless, one type of tissue frequently dominates other types and the cytologic appearances of sloughed cells will vary according to the degree of differentiation or lack of differentiation On this basis it is possible to divide the tumors into three types (1) very well differentiated or *squamous cell variety* (2) *moderately well differentiated type*, i e a tumor that grows in nests or sheets but with



Fig 165—Group of cancer cells in squamous formation from the secretions of a proved case of epidermoid carcinoma In two areas there is stratification but the surfaces do not contain cilia. The cells are fairly well differentiated. (Papanicolaou stain. $\times 200$)

out stratification or one in adenomatous formation and (3) a completely dedifferentiated type—the so-called oat cell carcinoma

Squamous Cell Carcinoma.—In the lung this arrangement of cancer tissue is the most frequently encountered In smears of bronchial secretions the cells are usually in groups of a few or in large sheets Their borders are almost always irregular but occasionally one surface is smooth (Fig 165) This is the free edge and unlike normal epithelium, which will often confuse the novice these collections of cancer

cells never display cilia. As a rule the cells are closely packed and the borders of the different cells are often difficult to outline. They vary considerably in shape and size. Some are quite small and others are large. When crushed on edge the cells toward the surface appear flattened and stratified, whereas the deeper ones are more polyhedral. The cytoplasm stains reddish brown to orange and, although the cytoplasm is abundant, the nuclear cytoplasmic ratio is slightly increased. The nuclei are round, oval or elongated, deeply and uniformly stained, and sharply defined. Despite their neoplastic nature, they are quite regular and do not exhibit the bizarre shapes and sizes seen in other cells to be described below.

When the cancer shows an abundant amount of keratinization the surface cells are found in considerable numbers in the secretions and present very characteristic appearances. Of these the most easily identifiable are epithelial pearls. They resemble closely the corresponding structures seen in histologic sections. Some are large but others are small. They are sharply circumscribed, round, and composed of concentrically arranged and compressed lunar-shaped epithelial cells. Their cytoplasm stains orange or occasionally a blue-gray, and the nuclei are compressed, pyknotic and very deeply stained. In addition to the pearls, numerous single keratinized cells are usually present. These are of many shapes and sizes. They are sharply defined and often round, and their cytoplasm is abundant and deep pink or orange. The nuclei are of odd shapes and sizes and extremely pyknotic. They are small in proportion to the amount of cytoplasm, compared with other cancer cells, but not quite so small as the nuclei of aspirated buccal cells with which they may be confused. Finally, in this first group there are almost always bizarre isolated cells similar to those so characteristically found in the second group.

Moderately Well Differentiated Type and Adenocarcinoma—When positive, the secretions from this type of tumor usually contain isolated cells or small groups of not more than a dozen. The latter are always rather loosely united and the individual cells are similar to the isolated ones. However they occur, the cells are so bizarre that it is virtually impossible to describe them all. They vary greatly in size and configuration. Some are no larger than neutrophils, others are ten to twenty times this diameter. They are round, oval, oblong, triangular, polygonal, spindle, and every other conceivable shape (Fig 166). Ordinarily their borders are not delineated by a distinct membrane but are rather fuzzy. The cytoplasm is almost always abundant, although in proportion to the size of the nucleus it is relatively decreased. Usually it stains gray or bluish gray with gradations from these to pink and occasionally orange. The nucleus is always absolutely and relatively enlarged. Usually it is single, but sometimes four or more nuclei are piled up on each other. The variations in

cells, but do not show the intense hyperchromatism or the clumping of the nucleoplasm seen in the cells of the second group. Single or multiple nucleoli are sometimes quite conspicuous, but often they are entirely absent.

Noncancerous Cells in Bronchial Secretions—Normally, and in diseases other than carcinoma, various types of epithelial and inflammatory cells are present. Ciliated columnar epithelium, cuboidal epithelium and basal cells can be readily recognized. The first are long and slender, with a flat surface covered with cilia, and with a long tapering base. The cytoplasm stains bluish green and the nuclei are



Fig 167—Smear of secretions from a proved case of completely dedifferentiated carcinoma showing seven cancer cells. They are all small but irregular, hyperchromatic and only two show a moderate amount of cytoplasm. In the others the cytoplasm is imperceptible. There are present also a few regular ciliated columnar cells, erythrocytes and neutrophils (Papanicolaou stain $\times 400$).

round or oval, and evenly stained. Cuboidal cells are very similar, except that they are shorter and many do not contain cilia. Basal cells are round or oval, they contain scanty bluish green cytoplasm and evenly stained round or oval nuclei similar in size to those of columnar or cuboidal cells. Often they are found singly, but at other times they are grouped into clusters. Very similar cells, except that they contain slightly more cytoplasm, are sometimes found in sheets, these we have previously termed intermediate cells. Sometimes (in pulmonary tuberculosis²) there are clumps or sheets of rounded, closely packed, rather bizarre-looking cells that look not unlike the squamous cells already described. In fact, they at first gave us considerable trouble in

deciding whether or not a lesion was cancer. No matter how irregular they may appear, fine focusing of the microscope will always disclose cilia and, when these are present they can definitely be labeled non-cancerous. Aspirated pavement cells from the buccal mucosa are large and polygonal, and stain pink or green. Their nuclei are relatively small, round and uniformly stained. There should be no difficulty in identifying inflammatory cells. Neutrophils and lymphocytes may be identified by their usual characteristics, and large mononuclear phagocytes frequently contain ingested material. Fibrin, carbon and other detritus are of no pertinent significance.

RESULTS

The following is a tabulation of our results as of May 1, 1946¹:

Proved cases of carcinoma	57
Diagnosed cytologically	47
Diagnosed by bronchoscopic biopsy	24
Diagnosed by stenosis, etc.	15
Secretions negative, bronchoscopy positive	4
Secretions positive, bronchoscopy negative	12

Of the total of fifty-seven cases of carcinoma of the lung studied, a cytologic diagnosis from bronchoscopically removed secretions was made in forty-seven, or 82.4 per cent. As a matter of fact, the more recent figures are even better, for of the last twenty-seven cases a positive cytologic diagnosis was made in twenty-five, or 92.5 per cent. On the other hand, cancer tissue was obtainable bronchoscopically in only twenty-four of the fifty-seven cases, or 42.1 per cent. Of most importance perhaps is the group of twelve cases diagnosed cytologically but in which bronchoscopy was completely negative. This group excites particular interest, for these are the cases that, when diagnosed early, are resectable and have the best chance of being cured.

SUMMARY

Most cases of carcinoma of the lung can be diagnosed by cytologic examination of bronchoscopically removed secretions. The technique is not difficult, and the results exceed those of any other single pathologic procedure known today. The method is highly recommended as an aid in the diagnosis of this most distressing disease.

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LABORATORY DIAGNOSIS IN THE ANEMIAS OF INFANTS AND CHILDREN

ALEX J. STEIGMAN, M.D.

DIAGNOSIS of the anemias of infants and children cannot be made merely from laboratory data. However, a careful study of blood will determine the presence and extent of anemia, and it will classify the anemia satisfactorily from a purely hematologic standpoint. It remains for the physician to determine the etiology, not only from these findings but also from careful examination and a detailed history, which may involve even antenatal history. This clinic will refer to classifications based on etiology as well as on hematologic morphology and make a correlation of these. The main emphasis will be on proper interpretation of usual laboratory findings. No technical methods of examination will be considered.

The anemias of infants and children have special etiologic factors, including the influences of maternal iron storage, prematurity, rapid growth, the exaggerated influence of infections, improper infant feeding, early appearance of hereditary forms of anemic disorders, the lability of hemopoietic responses and a difference in normal blood values at various ages. It is also noted that anemia develops more readily in infants and small children than in older children and adults; that the child's bone marrow reacts more readily to the anemia by freeing immature erythrocytes, and that splenomegaly is more frequent with the anemias of infants and children.

Recent advances in hematology have made it more important than ever to examine the blood of each anemic infant and child to permit proper classification of each case. No longer content to give transfusions for "low levels" and iron to all children, the pediatrician now stresses the periods of infantile life during which apparent anemia may be relatively normal, the futility of iron therapy in the face of persisting infection, the role of iso-immunization mechanism such as the Rh factor, the use of liver and synthetic folic acid in macrocytic syndromes and proper selection for splenectomy.

NORMAL BLOOD VALUES AT VARIOUS AGES 111118

Normally fetal blood in the latter portion of pregnancy is characterized by a high concentration of erythrocytes which are large (almost 9 microns in diameter) and contain more than normal iron.

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of hemoglobin. Many erythrocytes are immature, contain nuclei and reticular structure and have basophilic staining properties. At birth this tendency toward polycythemia persists and is manifested by relative macrocytosis, the presence of nucleated forms (0.01 to 0.05 per cent), and reticulocytosis (2 to 5 per cent). Owing to dehydration and to normal postnatal circulatory adjustments, the erythrocyte and hemoglobin levels often rise in the first forty-eight hours of life, and then decline in the ensuing two weeks, approaching normal adult values. Erythrocyte and hemoglobin levels then fall from the first

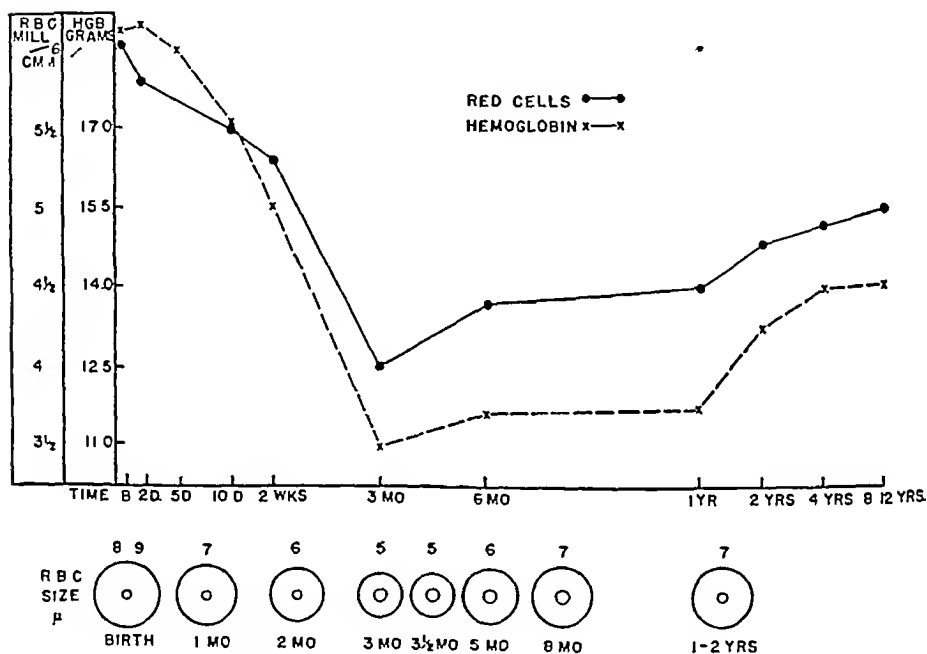


Fig 168—Norma blood values in infants and children. Note changes in size and in hemoglobin content of red blood cells producing microcytosis and hypochromia at ages of 3 to 3½ months with gradual recovery thereafter. (From L. K. Diamond in Mitchell-Nelson, Textbook of Pediatrics.)

month of life, reach their lowest level in the third to fourth months and return to normal by the eighth to ninth months of life. This is referred to as physiologic anemia of the newborn.

Physiologic Anemia of the Newborn—Microcytosis and hypochromia occur normally in young infants, being most marked in the third to fourth months of life (Fig 168). Such low grade anemia is quite normal and should occasion no anxiety unless such factors as superimposed infections or blood loss result in further depression of the levels. The erythrocyte count returns to normal a little more rapidly than does the hemoglobin level.

CLASSIFICATION OF ANEMIAS

No single classification can fit all clinical requirements. The ideal is an etiologic classification which also indicates the morphologic changes in erythrocytes. Since this is not possible we must simultaneously consider each anemic child or infant from the standpoint of etiology as revealed by clinical history and examination and confirmed by laboratory studies, and from the standpoint of hematologic findings. The lack of constancy of red cell alterations in infants and children makes it difficult to place much reliance on a classification based on cell volume and hemoglobin content. Thus the classification currently in favor is based primarily upon the broad principal mechanism of the disturbance, with an attempt at listing the specific etiology when it can be determined.

CLASSIFICATION AS BASED ON BROAD MECHANISM INVOLVED

- I. Anemias Occasioned by Excessive Demands on Supply of Blood (Bone marrow attempts to make up supply and is overactive)
 - A. Hemorrhage (Acute, Chronic Internal External Traumatic Hemostatic Defects)
 - B. Hemolytic States
 1. Constitutional or hereditary in origin
 - a. Hemolytic jaundice—congenital and acquired
 - b. Sickle cell anemia
 - c. Mediterranean anemia
 - d. Erythroblastosis fetalis
 2. Caused by chemicals e.g.
 - a. Benzol ring products
 - b. Lead
 3. Caused by systemic erythrolytic infections e.g.
 - a. Hemolytic staphylococci and streptococci
 - b. Malarial infestations
- II. Anemias Occasioned by Diminished Supply of Blood (Bone marrow is less active than normal.)
 - A. Deficiency of Items Required for Blood Formation (Exogenous, Endogenous)
 1. Iron
 2. Liver principle: folic acid (L. casel factor)
 3. Vitamins and unknown items
 - B. Suppression or Injury of the Bone Marrow
 1. Congenital aplasia or hypoplasia
 2. Toxic
 - a. Of various infections
 - b. In azotemia
 3. Chemical agents e.g.
 - a. Benzol ring products
 - b. Arsphenamine
 4. Myelophthisis e.g.
 - a. Leukemia
 - b. Neoplasms
 5. Physical agents e.g.

be distinctly lowered before the erythrocyte count is materially changed.

Anemia of Prematurity Immaturity—This anemia is characteristic of all immature infants, being proportionately more severe in the infants of lowest birth weights. It begins soon after birth and continues until about the third month of postnatal life, when spontaneous recovery sets in, a return to normal almost always occurs by the seventh month, barring complications such as infection. The anemia tends to

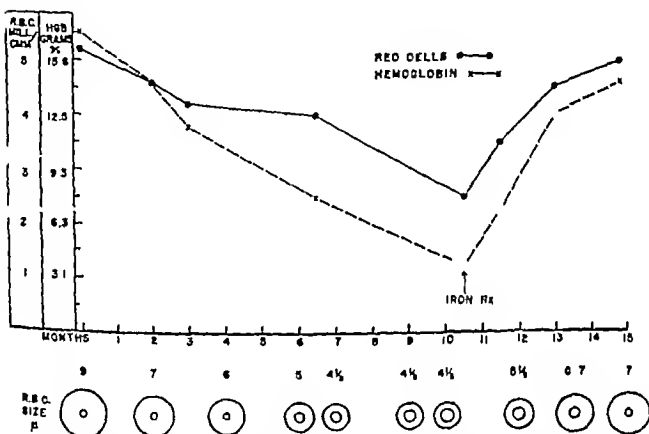


Fig. 170—Anemia, simple iron deficiency type. This infant was observed from birth through the fifteenth month of life. Soft solid foods were refused when offered at about six months of age. Anemia of moderate degree at 7 months, which progressed until admission to the hospital at 10 months of age. Rapid recovery followed oral administration of medicinal iron. Note the development of microcytosis and hypochromia during the first ten months and the improvement after treatment. (From L. K. Diamond in Mitchell Nelson: *Textbook of Pediatrics*.)

be normochromic until it reaches its low point at the third month of life, when spontaneous recovery sets in; the erythrocyte count rises more rapidly than the hemoglobin level, resulting in hypochromia, with a tendency toward microcytosis during this recovery phase. Reticulocytosis in the peripheral blood is seldom noted during this period. A relative lymphocytosis may occur during spontaneous recovery.

Macrocytic Anemia—The rigid criteria of pernicious anemia have been met in at least one case in a child, but its occurrence

extremely rare. However a macrocytic hyperchromic anemia may occur, viz

- 1 Chiefly in infants between 12 and 24 months of age, associated with a megaloblastic bone marrow, and achlorhydria, and responding rapidly to folic acid therapy or liver extract with reticulocytosis and a sustained rise in hemoglobin and erythrocytes²
- 2 With congenital malformations and with acute or chronic gastrointestinal disease or postoperative gastrointestinal shunts resulting in interference with absorption of liver extract principle

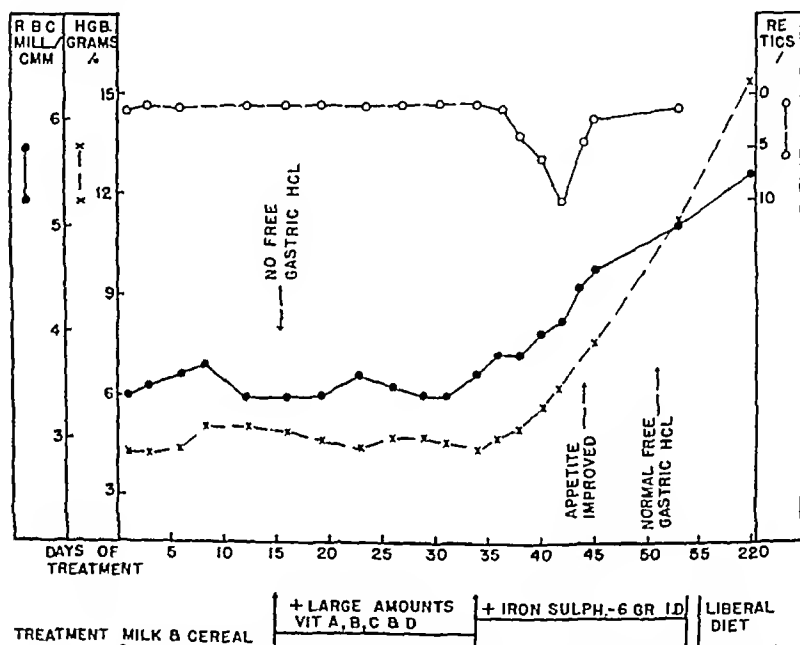


Fig 171—Anemia, iron deficiency type. Infant, 16 months of age, whose diet had been limited to cereal and milk. Anemia severe at time of entry to hospital. Gastric analysis showed no free hydrochloric acid. Treated for two weeks with large amounts of vitamin supplements, of which he had had very little. General improvement, but no change in blood levels or in percentage of reticulocytes. Improved rapidly following daily administration of 6 grains of ferrous sulfate. Reticulocyte peak of 10 per cent reached on tenth day. Appetite improved for all foods. Hydrochloric acid content of gastric juice became normal. (From L. R. Diamond in Mitchell-Nelson, Textbook of Pediatrics.)

- 3 With chronic and subacute liver disorders, such as so-called juvenile cirrhosis and leukemic infiltration of the liver
- 4 In association with temporary complete achlorhydria during febrile ailments (see No 1 above)
- 5 With tropical and nontropical sprue, very rarely in celiac disease (where the anemia is usually microcytic hypochromic)

The blood smear reveals macrocytosis and the reduction in hemoglobin is not so marked as the reduction in red cells. The color index is greater than 1 and the leukocyte count may be either elevated or slightly depressed.

Mediterranean Anemias (*Cooley's Anemia, Erythroblastic Anemia, Thalassemia, Target Cell Anemia*)—This type seen exclusively in offspring of families originating from Mediterranean countries, presents a slowly progressive anemia with splenomegaly and mongoloid facies due to changes in the bones of the skull and face.

An average case shows about 3 000,000 (or fewer) erythrocytes per cubic millimeter, the hemoglobin level is markedly depressed, giving

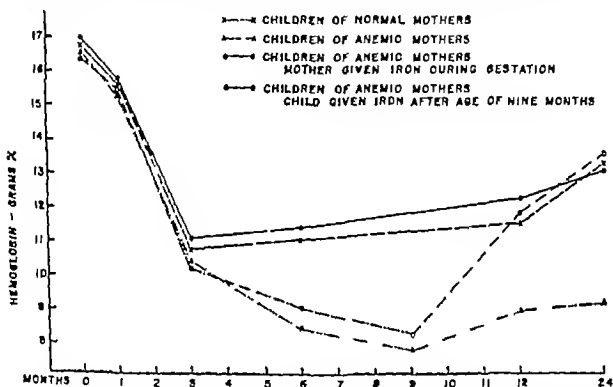


Fig 172.—Anemia in children of anemic mothers. Infants born to anemic mothers gradually develop severe hypochromic anemia after the third month of life. When treated with iron, recovery is rapid. If the mother is treated with iron in subsequent pregnancy the infant is protected against the development of this type of anemia. (From L. K. Diamond in Mitchell Nelson Textbook of Pediatrics.)

rise to a color index considerably below 1. Characteristically the blood smear shows a tremendous variety in size and shape of cells, from macrocytes of 12 to 14 microns to microcytes of 3 microns. Many early forms of erythrocytes are noted bearing nuclei, Howell Jolly bodies and Cabot rings, and exhibiting polychromatophilia, basophilic stippling and similar stigmas of immature red cells. "Target cells" characteristically macrocytes with unusual central and peripheral deposits of hemoglobin in band or target like rings are often seen.

The erythrocytes are more resistant to hypotonic saline than the normal controls, the serum bilirubin is elevated when examined by an

indirect van den Bergh test, and there is often a mild leukocytosis with a shift to the left of both granulocytes and lymphocytes

Congenital Hemolytic Anemia (*Familial Acholuric Jaundice, Spherocytosis, Hemolytic Ictero-anemia*)—This congenital and frequently familial form of chronic anemia with acute crises is believed due to an inherited defect in the hemopoietic system resulting in the production of fragile microspherocytic red cells. Microspherocytic cells occur also in acquired hemolytic anemias and can be produced ex-

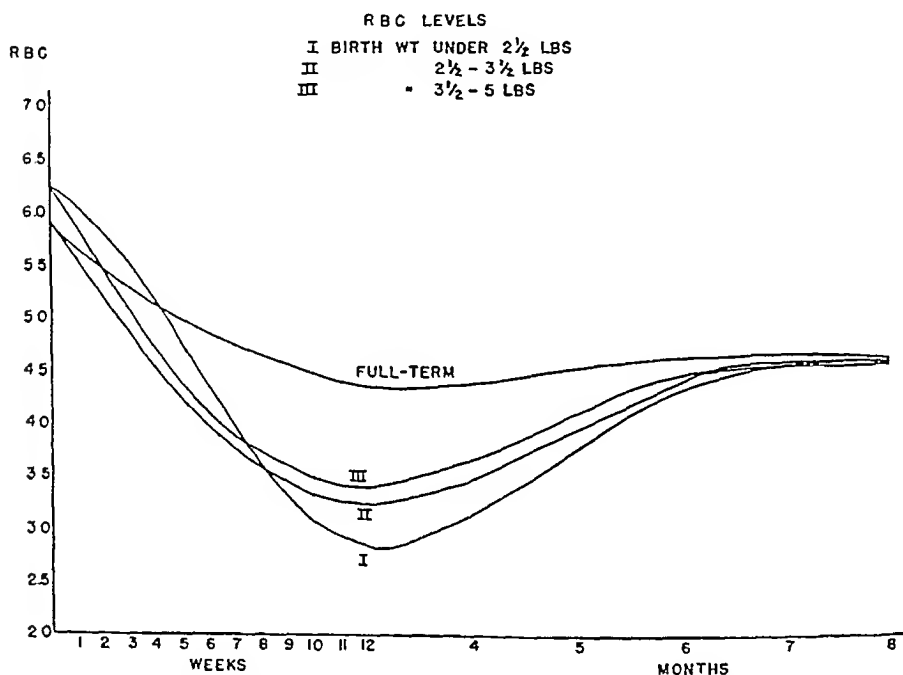


Fig 173—Anemia of prematurity. Comparison of red blood cell levels of full term infant with those of prematurely born infants of different birth weights. Note that the maximum severity of anemia in each group occurs at about 3 months of age but that the more immature the infant the more profound the anemia at this time. Eventual recovery of all groups at the same time, at about 7 months of age. (From L. K. Diamond in Mitchell-Nelson, Textbook of Pediatrics.)

perimentally by injecting hemolysins.³ During remissions the blood count may be virtually, if not actually normal, but during the so-called hemolytic crises it falls to dangerous levels. The color index is generally around 1, many of the erythrocytes are small and globular (microspherocytes) and a marked reticulocytosis is constant.

Fragility tests in dilutions of hypotonic saline solution reveal abnormal fragility so that hemolysis of red cells in this disease may begin in 0.50 to 0.85 per cent saline solution instead of at the usual level

of 0.45 per cent, and hemolysis may be complete in 0.40 to 0.50 per cent solution instead of in the usual 0.80 to 0.85 per cent. Tests for serum bilirubin show an increase varying with the severity and rapidity of the hemolytic crisis. Leukocytosis with marked shift to the left is frequent during the acute hemolytic crises and usually disappears during remissions. Splenectomy is the only treatment of merit, although this usually arrests the activity and prevents further crises, the microspherocytosis and the increased fragility may continue after the operation.

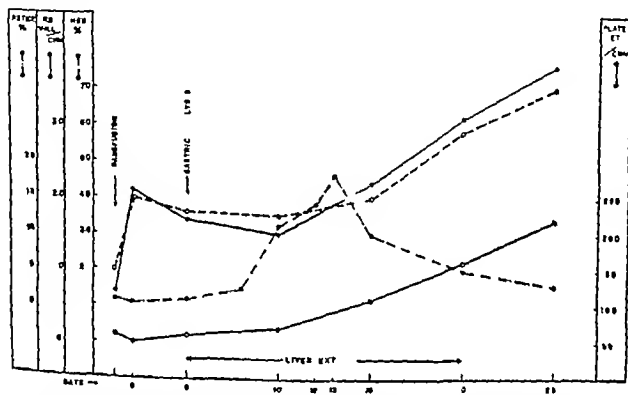


Fig 174.—Macrocytic anemia. Infant, aged 18 months with severe pulmonary infection of three weeks duration anemia was so severe that transfusion was given immediately upon admission to the hospital. Gastric analysis revealed no free hydrochloric acid and there was no response to histamine. Note the low level of blood platelets, which was associated with petechiae and a tendency to bleed. Liver extract was injected intramuscularly each day for a period of fifteen days with excellent results. reticulocyte count on the thirteenth day was 19 per cent; complete recovery by the twenty fifth day with return of normal blood values and normal gastric function. There was no subsequent recurrence of this anemia (From L. K. Diamond in Mitchell-Nelson, Textbook of Pediatrics)

Sickle Cell Anemia (*Drepanocytemia*)—This condition is congenital and hereditary and occurs almost exclusively in patients of Negro extraction usually manifesting itself in childhood. About 7 to 8 per cent of all Negroes have sickle cell anemia, i.e., erythrocytes which are sickle shaped when examined suitably but only about 10 per cent of these children show sickle cell anemia.

The characteristic cells are seen in fresh blood films from which after

is excluded by sealing with petrolatum. The erythrocytes assume the crescent or sickle shape in a few minutes to twenty-four hours. Characteristically, rapid sharp hemolytic crises occur and the hemoglobin and erythrocyte levels drop precipitously, maintaining a color index of approximately 1. There are signs of erythropoietic activity evidenced by polychromatophilia and by the presence of reticulocytes and occasional nucleated erythrocytes. With this, there is usually an increase in number of platelets and of leukocytes, the latter showing a shift to the left with immature forms. The icterus index is elevated on indirect van den Bergh test, and the erythrocytes show increased resistance to hypotonic saline. A recently devised test for determining the presence of activity in sickle cell anemia consists of contrasting the sedimentation rate of venous blood taken in the usual way with that of blood taken following the application of a tourniquet for ten minutes (or alternately by increasing the carbon dioxide tension in the blood specimen by mixing carbon dioxide with the blood in a flask). A difference of 20 mm between the sedimentation rate determined in the latter manner and that determined in the ordinary way indicates active sickle cell anemia.⁴

Erythroblastosis Fetalis (*Hemolytic Disease of the Newborn*) — Becoming apparent very soon after delivery, this disease may show a predominance, clinically, of edema, jaundice or anemia, and generally shows some elements of all three findings. Those with very marked edema are frequently stillborn or succumb quickly.

The characteristic blood finding is very large numbers of nucleated erythrocytes which appear very early and are accompanied by reticulocytes and nuclear fragments. The color index exceeds 1 because of the presence of macrocytes well filled with hemoglobin. A rapidly profound anemia sets in twelve to twenty-four hours after birth, the percentage of nucleated red cells may then diminish quickly, but the macrocytosis continues. A leukocytosis with many immature forms generally occurs, and in severe cases the platelets may be reduced to extremely low levels. Erythrocyte fragility in saline dilutions shows an increased span. The icterus index rises early and rapidly, and the serum reacts on both the direct and the indirect van den Bergh test.

Approximately 90 per cent of infants with this form of anemia are Rh-positive, the mothers are Rh-negative and the fathers Rh-positive, either heterozygous or homozygous. The mother's serum generally shows anti-Rh agglutinins, and the titer may increase for ten to fourteen days after delivery. Special tests of maternal serums may show inhibiting or blocking anti-Rh antibodies when the usual demonstration fails. On the other hand, about 10 per cent of the cases are due to intragroup iso-immunization entirely unrelated to the Rh factor.

but caused by subtype iso-immunization with the major blood groups O A B and AB² The mechanism is similar to that in the Rh induced cases and the genetic implications of mating are similar

Acute Hemolytic Anemias—These anemias present a variable picture of clinical symptoms and blood findings, produced by a variety of etiologic factors, including toxins of infections, such drugs as sulfonamides and endogenous isohemolysins of unknown source, perhaps mediated by the spleen. The group includes variations from the so-called Lederer's anemia, with its abrupt onset and rapid cessation following transfusion, to recurring and chronic forms closely resembling congenital hemolytic anemia and, like it, responding to splenectomy.

The blood picture is modified by the severity and rapidity of the process. The erythrocyte count varies from four to one million with the hemoglobin level proportionately slightly lower in some instances. The blood smears reveal many macrocytes and many young forms with numerous reticulocytes, exhibiting fragmentation and polychromatophilia. Erythrocyte fragility varies being chiefly normal in acute cases and being increased in the chronic recurring varieties. There is usually a concomitant leukocytosis with numerous young myeloid forms. Thrombocytosis is also frequent. Hemoglobinuria early in the illness may mark the acute Lederer's type. Elevated urobilinogen levels in both stools and urine are frequent laboratory findings. The intensity of the icterus index varies proportionately with the severity of the illness.

Aplastic Anemia.—This classification refers to a general reduction of red cells, white cells and platelets in the peripheral blood, and, because all the three formed elements are involved the syndrome should properly be called panhematopenia. Inability of the bone marrow to produce these three elements may come from a detectable cause, such as severe nutritional deficiency, roentgen ray or benzol ring intoxication and bone marrow replacement by tumorous and leukemic tissue or it may occur without detectable cause. In children unfortunately, the latter or idiopathic variety is the more common type.

The blood shows a normocytic normochromic anemia, with levels which may easily drop to 1,000,000 erythrocytes and to 3 or 3.5 gm of hemoglobin. There are no young forms of erythrocytes, i.e., no signs of regeneration. The granulocytes are reduced, resulting in leukopenia with relative lymphocytosis. The platelets are reduced markedly, resulting sometimes in prolonged bleeding time and absence of clot retraction.

Congenital Hypoplastic Anemia.—This is a chronic anemia appearing usually within the first three months of life and having no apparent cause such as prematurity, infection or maternal anemia. It

TABLE 1—RANGE OF COMMON LABORATORY FINDINGS IN TEN COMMON FORMS OF ANEMIA IN INFANTS AND CHILDREN,
AS SEEN IN UNRELATED CASES

(The range varies with severity, duration, specific etiology and coexistence of multiple etiologic factors)

Clinical Type	Hemo- globin Gm	Red Blood Corpuscles Millions	Usual Color Index	Special Types of Red Blood Corpuscles	Reticu- locytes	Fragility in Saline	Tolerus Index	Special Studies	White Blood Cor- puscles	Platelets
Physiologic anemia of newborn	11.0 to 10.5	5.0 to 1.0	< 1.0	Pale micro- cytes	N	N	-	-	N	N
Iron deficiency anemia	10.0 to 1.0	4.5 to 1.0	< 1.0	Pale micro- cytes	N	N	-	-	N to -	N
Anemia of prematurity	10.0 to 6.0	1.0 to 2.5	1.0 to < 1.0	Nono	N	N	-	-	N to -	N
Macrocytic anemia syndrome in infants	10.0 to 3.5	3.0 to 1.0	> 1.0	Macrocytes	+	N	-	May have tem- porary gastro achlorhydria	Varies	N to -
Mediterranean (Cooley's anemia)	8.0 to 3.0	3.0 to 1.0	< 1.0	All stages of development, target cells	+	-	+	-	+	N
Congenital hemolytic anemia	10.0 to 3.0	1.0 to 1.0	1.0	Microspher- ocytes	+	+	+	For isohemoly- sins	+	N to +
Sickle cell anemia	11.0 to 5.0	1.0 to 1.0	1.0 to < 1.0	Sickle cells	+	N to -	+	Sickling prepa- ration	+	N to +
Erythroblastosis fetalis	17.0 to 5.0	5.0 to 1.0	> 1.0	Many nucle- ated	+	Varies	+	90% show Rh iso-immuniza- tion	+	-
Acute hemolytic anemia	10.0 to 3.0	1.0 to 1.0	Varies	Young forms	+	Varies	N to +	Varies with eti- ology	+	N to +
Congenital hypoplastic anemia	11.0 to 5.0	1.0 to 1.0	1.0	Nono	N to +	N	-	-	-	N

N normal + increased - decreased

is important to recognize this condition early, because normal growth and development of the infant depends upon administration of transfusions as needed, usually every two months

Laboratory examination shows a normocytic normochromic anemia, with erythrocyte counts even as low as 1 000 000 cells. Feeble attempts at regeneration are indicated by a mild reticulocytosis of 1 to 2 per cent, and bone marrow reveals hypoplasia with immaturity of erythrogenic cells. The leukocyte count may be slightly reduced but rises in response to infection, the platelet count is normal, distinguishing this condition from true aplastic anemia.

Splenic Panhematopenia of Doan—Superficially resembling aplastic anemia, this uncommon condition can be differentiated by laboratory methods; such differentiation is important because splenectomy results in complete remission.⁶

Laboratory examination of peripheral blood will show low levels of erythrocytes, leukocytes and platelets, the degree of depression varying with the severity and the relative acuteness of onset. Injection of epinephrine produces an abrupt, though transient, rise in all three formed elements of the blood. The hyperplasia revealed on examination of the bone marrow distinguishes this condition from aplastic anemia.

SUMMARY

Anemias of infants and children require special consideration because of special etiologic factors and hemopoietic instability. The closest possible correlation between clinician and clinical pathologist must exist in order for each case to be properly classified according to the underlying causative mechanism.

The normal blood values differ at various age levels, the newborn having what appears to be polycythemia and the 3 to 5 month old infant having what appears to be a microcytic hypochromic anemia. Familiarity with normal levels is essential.

The commonest form of anemia is due to iron deficiency from a host of causes. When infection coexists, iron therapy fails until the infection is eradicated.

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RECENT ADVANCES IN THE KNOWLEDGE OF "VIRUS HEPATITIS"

JOHN R. NEEFE, M.D. *

At the beginning of World War II the disease now recognized as "homologous serum hepatitis or jaundice" was relatively unknown to the medical profession, and information concerning "infectious hepatitis" was remarkably limited in view of the fact that apparently it had been a problem of some military importance during nearly all the major conflicts of the last century and, in some countries, a major public health problem during times of peace. The factors associated with these two diseases during the recent war—their high incidence and significant mortality, the relatively long period of disability extended illness as a result of relapses or the development of a chronic form of the disease, lack of knowledge of the etiological agents and their modes of transmission, and lack of specific methods for diagnosis, treatment, prevention and control—all led to extensive investigations both in this country and abroad. The results of these investigations have provided new knowledge concerning many aspects of these diseases. As the reports on these advances are scattered widely throughout the literature and some confusion in their interpretation apparently exists, it has seemed desirable to assemble some of the accumulated data in an attempt to clarify the current concepts of these diseases.

To avoid the confusion resulting from the lack of an adequate and standard nomenclature, and because the etiological agents of the types of hepatitis under consideration have many properties which justify their tentative classification as viruses, the term "virus hepatitis" will be used in reference to this group of similar diseases. "Virus hepatitis" thus includes both *infectious hepatitis* (which probably is identical with or closely related to the diseases referred to in various parts of the world as "catarrhal jaundice," "epidemic hepatitis or jaundice," "infective hepatitis" and "hepatitis epidemica") and

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homologous serum hepatitis (probably identical with or closely related to the diseases variously referred to as "transfusion jaundice," postvaccinal or vaccinal jaundice or hepatitis," "postinoculation or inoculation jaundice or hepatitis," "syringe hepatitis or jaundice," and probably so-called "late postarsphenamine jaundice")

ETIOLOGY

None of the etiological agents of "virus hepatitis" studied to date has been seen with the ordinary or electron microscope,^{1,2} and definite propagation in ordinary culture mediums, tissue culture or chick embryos has not been observed.^{3,4} No successful transmissions to species other than man have been accomplished,^{3,5,6,7,8,9,10} although suggestive but unconfirmed evidence of transmission to pigs,¹¹ the developing chick embryo,^{12,13} birds^{14,15} and rats¹⁶ has been reported. The lack of definitely susceptible laboratory species, one of the chief hindrances to progress in the investigation of these diseases, has necessitated the use of human volunteers for most of the basic studies. Attempts to develop serological or other tests *specific* for the etiological agents also have been unsuccessful.^{3,9,17,18} At the present time, therefore, the only method of demonstrating the presence or effect of various procedures on a hepatitis virus in a given material requires the use of human volunteers. The limited experimental knowledge of the antigenic properties of these viruses also has been derived indirectly from studies of the resistance of volunteers to infection with the same or different strains of hepatitis virus after recovery from an initial infection with a known strain. In spite of the lack of adequate numbers of human volunteers and specific methods for laboratory investigations, considerable information concerning the properties of the etiological agents has been obtained.

Hepatitis viruses have been shown to pass through Seitz, Berkefeld, Chamberlain and other bacteria-retaining filters.^{8,9,10,20,21} They have survived heat at 56°C for at least 30 to 60 minutes,^{3,8} and have remained active for at least several years in frozen materials (often thawed and then refrozen during the interval)²² and in materials stored at 4°C.⁹ One in desiccated yellow fever vaccine was active after storage for one year at room temperature in Washington, D. C.²³ Hepatitis viruses have survived for months in serum containing merthiolate in concentration of 1/2000,²¹ in a mixture of equal parts of phenol and ether in a 0.5 per cent concentration,¹⁰ and in a 0.2 per cent concentration of tricresol.³ Studies of the resistance to chlorine of a hepatitis virus in experimentally contaminated water suggested that it may be more resistant to chlorine than the bacterial pathogens commonly encountered in drinking water.²⁴ On repeated occasions hepatitis viruses have been passed in series from one human to another by inoculating with mate-

nals collected from the preceding subject,^{3 6 8 9 20 23 25 26} indicating their infectious nature. These observations provide the basis for the tentative classification of these agents as viruses and show that they possess a high degree of resistance to processes which inhibit or destroy most bacteria.

The suggestion that more than one virus might be concerned in the problem of virus hepatitis came with the recognition of so-called *homologous serum hepatitis* the causative agents of which, for convenience, will be referred to as *virus SH*. A distinction between this type of hepatitis and the naturally occurring disease, *infectious hepatitis* (the causative agents of which subsequently will be referred to as *virus IH*), was first suggested by fairly consistent differences in the length of the incubation period, some of the clinical manifestations associated with the onset of the disease, and the frequency of secondary cases among contacts.⁷ The results of subsequent experimental studies in human volunteers confirmed the first two differences and, in addition, revealed others of significance.

Virus SH Hepatitis.—Experimental studies in volunteers of viruses (virus SH) considered to be representative of characteristic homologous serum hepatitis have revealed the following

1 The interval between parenteral injection of this virus and the onset of acute hepatitis usually has been between two and four and one-half months.^{3 8 9 22 23 28}

2 The onset usually has been without fever or with fever that seldom exceeded 100 F (oral).^{22 28} Although this has been consistent in the experimentally induced cases fever apparently has been more prominent in some cases observed during outbreaks of the disease.

3 The virus has been demonstrated in the blood stream of an inoculated volunteer as long as eighty-seven days before the onset of acute hepatitis and has usually been present during the early stages of the active disease.^{23 28} Adequate data concerning the length of time this virus persists in the blood after the onset of hepatitis or concerning its presence in subclinical cases are lacking.

4 All attempts to demonstrate this virus in the feces of infected persons have been unsuccessful.^{23 29 30} but the possibility has not been excluded.

5 Data concerning the presence of this virus in nasopharyngeal secretions also have not been conclusive.^{22 30} Some evidence suggesting its presence in these secretions has been obtained,³¹ but confirmation is lacking.

6 The single attempt to demonstrate this virus in the urine of infected persons was unsuccessful and does not warrant conclusions.²⁸

7 After recovery from an infection with this virus, volunteers were found to be resistant to reinfection with the same virus for a period of up to eighteen months. No experimental studies concerning resistance for longer periods have been made.^{22 28 32}

8 After recovery from infection with this virus, volunteers were susceptible, possibly more susceptible than normal persons, to infection with the virus of the naturally occurring disease (*virus IH*).^{22 28 33}

9 Oliphant's⁹ studies suggested that this virus is the serum or yellow fever vaccine may have been inactivated by exposure to ultraviolet light (YFV—one hour at 2650 Angström units and one and one-half hours at 2537 Angström units serum—forty five minutes, 85 per cent 2537 Angström units)

10 Except for one experiment^{3a} in which the disease apparently was induced in two volunteers by the intranasal administration of a serum presumably containing a strain of this virus, efforts to induce hepatitis by the oral administration of scrums containing virus SH, which were highly effective in inducing the disease when injected parenterally, have failed.^{22 26, 28} This indicates the importance of including the parenteral route when testing for the presence of this virus and renders negative results obtained with other routes of administration (i.e., nasopharyngeal or oral tests of nasopharyngeal secretions, feces and urine) of less significance.

Virus IH Hepatitis.—*Studies in human volunteers of viruses considered to be representative of the naturally occurring disease (infectious hepatitis, virus IH) have revealed the following*

1 The interval between oral inoculation with this virus and the onset of acute hepatitis in volunteers usually has been between seventeen and thirty-seven days^{8, 22 35 36, 37} The interval from parenteral inoculation of volunteers with strains of virus considered to be representative of virus IH to the onset of acute hepatitis has been less consistent. With strains obtained in Pennsylvania²² and Sicily⁸ it consistently was within the range (less than forty days) observed after oral inoculation with the same virus. With another strain apparently obtained in the Mediterranean area, the interval ranged from thirty-eight to forty-three days.³⁴ Other investigators have reported experiments in which the interval was as long as four months^{5, 32, 35} However, because other data concerning the behavior of these strains of virus associated with the longer interval either were not available or not specifically described, and because their consideration as strains of virus IH apparently was based on the history of the cases from which they were obtained, the possibility that they actually may have been strains of virus SH cannot be excluded.

2 The onset of acute hepatitis induced by virus IH has usually been abrupt and associated with fever.²²

3 The virus frequently has been demonstrated in the blood during the early stages of the active disease,^{8 22, 36} and some evidence indicates that it may be present in the blood during the incubation period before the onset of symptoms.³⁴ Studies on the length of time the virus persists in the blood have been too limited to warrant conclusions.

4 The virus has been demonstrated repeatedly in the feces of patients with the active disease, irrespective of whether the route of entry was oral or parenteral.^{8 22, 35, 37 38 29} Studies on the length of time the virus continues to be excreted in the feces have been too limited to warrant conclusions. With the exception, however, of a suggestive but inconclusive transmission with feces obtained from chronic nonicteric cases after the subsidence of jaundice,⁴⁰ attempts to demonstrate the presence of the agent in feces after the disappearance of jaundice have been unsuccessful.³⁹

5 Attempts to demonstrate the virus in the nasopharyngeal secretions obtained during the active disease^{20 22 35 41} have been unsuccessful, although one suggestive but inconclusive result has been obtained.³⁵ But since adequate studies have been limited to specimens obtained during the preicteric or icteric stage, these negative results do not permit conclusions regarding the infectivity of the nasopharyngeal secretions during the incubation period prior to the onset of the disease.

6 Except for two suggestive results,^{36 37} attempts to demonstrate the presence of the virus in urine obtained from volunteers during the active disease have been unsuccessful.^{20 22 35 41}

7 After recovery from infection due to virus IH, volunteers were found to be resistant to reinfection with the same virus for periods of up to one year.

No experimental studies covering intervals beyond one year have been reported^{20 22 23 28 41}

8 After recovery from infection with virus IH volunteers were found to be susceptible to infection with virus SH^{22 23}

9 One of the strains of virus IH which was highly effective in inducing hepatitis when administered orally was found to be relatively ineffective in inducing hepatitis in normal persons when administered parenterally. In contrast, this same virus was highly effective by the parenteral route in volunteers who had recovered from hepatitis due to virus SH indicating not only a lack of cross immunity but also a greater than normal susceptibility to virus IH presumably as a result of the previous infection with virus SH^{25, 26}

10 Normal volunteers who failed to develop hepatitis after parenteral injection of virus IH probably were immunized by an inapparent infection, the volunteers being resistant to a subsequent oral challenge inoculation with this virus²². The result apparently provides experimental evidence of protective active immunization by inapparent infections with virus IH

The experimental data cited above, particularly those indicating a lack of cross immunity, have provided evidence that viruses SH and IH, although probably closely related, are not identical. It is apparent, therefore, that at least two strains or types of virus are concerned in the problem of virus hepatitis. Most of the hepatitis viruses studied to date appear to be similar to either virus IH or SH.* The fact that one strain of virus IH has been relatively ineffective when administered parenterally to normal volunteers,²² whereas others^{9 34} apparently have been as effective parenterally as orally may be indicative of the existence of more than one strain or substrain of virus IH. This also might account for some of the differences in the incubation period noted in connection with parenteral injection of viruses considered to be strains of virus IH although we cannot exclude the possibility that those associated with incubation periods as long as four months were strains of virus SH rather than IH.

Classification of Virus Hepatitis—The obvious confusion that exists in connection with the identity of the hepatitis viruses used in some of the various experimental studies indicates the need for an improved classification of such viruses. Although a satisfactory classification will not be possible until methods for more specific identification of these viruses are discovered the author has found the following simplified tentative classification of virus hepatitis based on the existing etiological and epidemiological knowledge, useful.

I *Virus Hepatitis* Used when sufficient data are not available to justify more specific classification as II or III. When justified by the available data, may be subclassified as follows:

- A *Epidemic*
- B *Sporadic*

* Sufficient evidence is not yet available to clarify the exact relationship between viruses IH and SH. Thus they simply may be different strains of the same virus or more distinct types such as influenza viruses A and B.

- II *Virus IH Hepatitis* Those types in which the syndrome and epidemiological features are similar to those described in connection with virus IH. So-called infectious hepatitis, epidemic hepatitis, catarrhal jaundice and hepatitis epidemica are included under this heading
- A *Epidemic*
B *Sporadic*
- III *Virus SH Hepatitis* Those types in which the syndrome and epidemiological features are similar to those described in connection with virus SH. So-called homologous serum hepatitis or jaundice, transfusion jaundice, postvaccinal or vaccinal jaundice, postinoculation or inoculation jaundice, syringe-transmitted hepatitis and delayed or late arsenotherapy jaundice are included under this heading
- A *Epidemic*
B *Sporadic*

In this classification hepatitis caused by a virus known to have characteristics similar to those of virus SH is designated as virus SH hepatitis, and hepatitis due to a virus known to have properties similar to those of virus IH is referred to as virus IH hepatitis. When sufficient data are not available to justify such specific classification, as is frequent except under certain epidemic or other special conditions, the general term "virus hepatitis" appears preferable, as the newer knowledge concerning the methods of transmission of hepatitis viruses has indicated that specific classification on the basis of the history of the individual case is unreliable. Classification on this basis (history) undoubtedly has led to designation of some cases as infectious (virus IH) hepatitis that actually are due to virus SH, likewise, some cases of homologous (virus SH) hepatitis undoubtedly have been designated as infectious (virus IH) hepatitis. This is particularly likely to occur because both virus SH and virus IH can be transmitted by blood, plasma or serum. Thus, if the term homologous serum hepatitis is to be used for any type of virus hepatitis in which the agent has been transmitted by parenteral introduction of blood or blood products, the existence of these two apparently etiologically distinct types should be recognized. Furthermore, the absence of a history of previous injection of blood or blood products does not necessarily indicate that the disease is naturally occurring (not parenterally acquired) infectious (virus IH) hepatitis. Recent data strongly suggest that either virus IH or SH may be transmitted by improperly sterilized syringes and needles used only for withdrawal of blood or for parenteral injection of materials of any type.^{42 43 44 45 46} Such procedures, often performed on large groups of persons for prophylactic, diagnostic or therapeutic purposes, may be overlooked as sources of infection with either virus. Subsequent hepatitis developing in such persons thus may be regarded erroneously as a naturally occurring (not parenterally acquired) infectious (virus IH) hepatitis because there is no history of a previous injection of a blood product. For

these reasons, specific classification of individual cases as infectious (virus IH) hepatitis or homologous serum (virus SH) hepatitis, with the resulting implication concerning the etiological agents, is likely to lead to confusion and difficulty in interpretation of data. Such tentative classification is desirable, however, when sufficient data on the behavior of the virus in human beings are available to indicate a similarity to virus SH or virus IH.

EPIDEMIOLOGY

Geographic Distribution—Due to the lack of a specific diagnostic test, the exact geographic distribution of infectious (virus IH) hepatitis has not been defined. The data suggest, however, that no climatic or environmental limitations exist and that this disease occurs throughout the world.^{8, 20} The recognition of homologous serum hepatitis (virus SH) has been so recent that its geographic distribution is even less well defined. Available reports, however, suggest that it too may be wide.⁴⁷

Season—Virus hepatitis may occur in sporadic or epidemic form at any time of the year. Infectious hepatitis however has been noted to have a seasonal trend, increasing numbers of cases tending to occur during the fall and early winter followed by a decrease in incidence during the late winter and spring.^{48a} Explanations for this seasonal trend are not apparent.

Race.—No definite racial insusceptibility has been noted. Negro United States Army troops, however have been observed to be more resistant to infectious (virus IH) hepatitis than associated white troops.⁴⁹ The data of Fox et al.¹⁸ suggest that Brazilian Negroes were less susceptible to postvaccinal (virus SH) hepatitis than whites. It appears possible that the environmental factors in early life may differ in such a way that certain races as a whole may develop an acquired resistance earlier in life than some other races. The existence of a constitutional factor however, is possible.

Sex.—The available information suggests that both sexes are equally susceptible to virus IH.^{9, 20, 50} However an etiologically obscure form of hepatitis (virus), affecting chiefly women of menopausal age, recently has been recognized in Denmark.⁵⁰ Pregnancy does not appear to decrease susceptibility. The only two pregnant women exposed during one epidemic of virus IH hepatitis both developed the disease.⁵¹ In these two instances, in which the infections were acquired during the third month of pregnancy the subsequent course of the pregnancies was uneventful and both infants apparently were normal at birth. Whether or not pregnancy increases susceptibility has not been determined. In the Brazilian outbreak of virus SH hepatitis described by Fox et al.,¹⁸ the incidence was somewhat higher in males than females.

The age distributions, however, were not mentioned, a factor which might account for the difference noted

Age—Age has been shown to be an important factor in susceptibility to infectious (virus IH) hepatitis. Suitable data for an analysis of the effect of age on susceptibility to this disease are available from the study of an epidemic that occurred in a Pennsylvania camp for boys and girls during the summer of 1944.^{*} Other data on this epidemic have been reported elsewhere.²⁰ As the virus was water-borne, it is reasonable to assume that the entire camp population was exposed. The total incidence of apparent infections was known, the data indicated no difference in sex susceptibility, all were of the same race, and, because of the rapid progress of the epidemic, it is reasonable to assume that the virulence of the virus did not change significantly during the time involved. These and other data suggest that age was the principal factor governing the incidence of apparent infections in this epidemic.

The data on total incidence of hepatitis by age groups and those on the distribution of icteric and nonicteric cases in the various age groups are presented in Table 1. On the basis of total incidence (including hepatitis with and without jaundice) we see that (1) The total incidence was highest among those between the ages of 6 and 25, the mean incidence for the four subgroups (6 to 10, 11 to 15, 16 to 20, 21 to 25) being 72.6 per cent. As the total incidence in each of the four subgroups was not significantly different, they have been combined for statistical comparison with the other groups. (2) The total incidence in the 1 to 5 group (majority between 3 and 5) was only 37 per cent, almost 50 per cent lower than that of the 6 to 25 age group. This difference, when tested by the Chi square method, is highly significant statistically and appears to indicate that children under 6 are much less susceptible than persons between 6 and 25 years of age. (3) The susceptibility of those between 26 and 30 was somewhat greater than that of persons over 30, although the difference is not statistically significant. (4) The susceptibility of those over 26 was considerably less than that of persons between 6 and 25, the difference being highly significant statistically. These data provide strong evidence that susceptibility to this disease is high between the ages of 6 and 25 and rapidly decreases after 25. Probable explanations for this decrease in susceptibility with advancing age will be considered under the discussion of immunity. An explanation for the lower susceptibility of children under 6, who appeared to have approximately the same degree of resistance as persons over 26, is not apparent. The interval is much longer than that usually considered compatible with passively acquired maternal immunity. Constitutional factors may possibly be involved.

The data on the incidence of nonicteric as compared with icteric cases also reveal significant differences in the various age groups. Statistical analysis on this basis permits a comparison of the 1 to 10, 11 to 30, and over 30 age groups, the differences observed within the subgroups comprising each of these three groups not being significant. The data reveal the following: (1) Of those between the ages of 1 and 10 who had apparent infections, 40 per cent had the nonicteric

^{*} Represents work done under the Commission on Measles and Mumps, Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, U. S. Army, Washington, D. C.

form of the disease (2) The incidence of the nonicteric form in those with apparent infections between 11 and 30 was much lower the mean incidence being only 12 per cent. (3) The incidence of the nonicteric form (77 per cent) among the few over 30 years of age who developed apparent infections was surprisingly high (4) The higher incidence of the nonicteric form among those under 11 and those over 30 represents highly significant differences statistically from the relatively low incidence of nonicteric infections among those between 11 and 30 The observations on total incidence and the ratio of icteric to nonicteric cases thus

TABLE 1 —DATA SHOWING RELATIONSHIP OF AGE TO RESPONSE TO INFECTION WITH HEPATITIS VIRUS IH DERIVED FROM STUDY OF A WATER BORNE EPIDEMIC OF INFECTIOUS HEPATITIS THAT OCCURRED DURING 1944 IN A PENNSYLVANIA SUMMER CAMP FOR BOYS AND GIRLS

(The table shows the total incidence of apparent hepatitis in each age group and the percentages of this total provided by hepatitis with overt jaundice and by hepatitis without overt jaundice)

Age		Incidence Infectious (virus IH) Hepatitis			
Range	No	Total		Jaundice	No Jaundice
		No	%	Per cent of Total	Per cent of Total
1-5	27	10	37.0	60	40
6-10	174	126	72.4	59	41
11-15	154	121	78.6	83	17
16-20	79	51	64.6	88	12
21-25	32	24	75.0	83	17
26-30	11	4	36.4	100	0
Over 30	48	6	12.5	33	77
Total	525	342	65.1	74	26

provide mutually confirmatory evidence of the importance of age in the response to infection with virus IH. The most marked transitions in this response appear to be in the 6 to 10 and 26 to 30 age groups. Thus, although the total incidence rose sharply in the 6 to 10 age group, the number of nonicteric cases was relatively high and suggests that, although the total incidence was similar, the general resistance of this group was somewhat greater than that of persons between 11 and 25 in whom susceptibility appeared to be maximal. Although there appears to be a difference in the ratios of icteric to nonicteric cases of the 26 to 30 and over 30 age groups, this difference is not significant statistically and the data thus are compatible with the concept, indicated by the total incidence, of an increase

in group resistance to infection with this virus after the age of 26. In a study of the age incidence of infectious hepatitis in the United States Army troops in the Mediterranean Theater of Operations, Gauld^{48b} also obtained evidence of a definite increase in the resistance of groups over 30 years of age as compared with those under 30.

These data showing the variation in response to infection with virus IH of different age groups appear to have important epidemiological and clinical implications. As the nonicteric cases frequently are not recognized and thus not subjected to any form of control, they undoubtedly are of importance in the spread of the disease. The 6 to 10 age group would appear to be of particular importance in this respect. The observations also provide a possible explanation for the difference in morbidity of the disease observed in children as compared with that in persons of military age (see "Morbidity and Mortality").

Adequate data are not yet available for definition of the relationship between age and *homologous serum (virus SH) hepatitis*. However, the available data provide no evidence of a decrease in susceptibility with advancing age. In fact, the data of Oliphant⁹ and of Fox et al.⁷⁸ obtained from the study of outbreaks of postvaccinal (virus SH) hepatitis in the Virgin Islands and Brazil respectively, showed the incidence to be slightly higher in persons between 20 and 70 than in those under 20 years of age. If confirmed, this will constitute a further difference between virus IH and virus SH hepatitis.

Incidence—Apparently sporadic cases of virus hepatitis frequently are encountered, one or more cases usually being present throughout the year on the medical wards of most large hospitals. Numerous epidemics of infectious (virus IH) hepatitis have been reported in the literature, and during the war years were frequent and involved both civilian and military populations.^{8, 52} In the Mediterranean area alone, in which tens of thousands of cases occurred in United States Army troops (and in those of other nations as well), Gauld^{48a} reports that the case rate in certain military units occasionally was so high as to involve 40 to 50 per cent of the total command. In the Pennsylvania summer camp outbreak in 1944,²⁰ 65 per cent of the total camp population acquired the disease within a period of seven weeks. It is evident that infectious hepatitis may be classified as a common disease of great public health importance, exclusive of the nonicteric cases which undoubtedly would considerably increase the total incidence. The disease has recently been made reportable in some states and a more precise indication of the true incidence in this country may become available from accumulated facts of this type.

Although data on the incidence of homologous serum (virus SH) hepatitis are even less adequate, it also appears to have been high during recent years. In United States Army troops during 1942 over

23,000 cases followed the administration of certain lots of yellow fever vaccine that apparently also contained virus SH.³⁴ It has not been possible to estimate the number of cases resulting from the large scale use of blood and plasma transfusions during the war years, but many cases of what appears to be this disease have been observed in battle casualties.³⁵ In civilian hospitals also the disease apparently is being recognized with increasing frequency.^{43, 46, 51} There is reason to believe, therefore, that the disease may be commonly encountered and constitute an important public health problem of the future. Whether it occurs in epidemic or sporadic form obviously depends on the number of persons who receive infective material parenterally.

Morbidity and Mortality—The apparently low morbidity of this disease in children has led to the idea that infectious (virus III) hepatitis is a relatively innocuous disease. Although this may be true in children, in persons of military age it is a disease of high morbidity. According to Gauld,^{48a} among United States Army soldiers in the Mediterranean Theater, it was the greatest cause of disabling illness and resulted in a greater loss of effective man power (due to the relatively long period of disability, which averaged approximately sixty days) than malaria. The mortality fortunately appears to be low, apparently being approximately 0.2 per cent. In some epidemics, principally involving children, there has been no mortality,⁵⁰ this again possibly being related, in part, to age. The general condition of the patient before the onset and differences in the virulence of various strains of virus also may be related to the mortality. Because of the high incidence however, Gauld^{48a} states that it was one of the principal medical causes of death among United States Army troops in the Mediterranean Theater despite the low mortality rate.

The morbidity of homologous serum (virus SH) hepatitis apparently is at least as great as that of infectious (virus III) hepatitis. The mortality has varied from 0.2 per cent, reported for the 1942 United States Army outbreak after yellow fever vaccine inoculations, to estimates of much higher figures (6 to 19 per cent) for some smaller outbreaks related to other materials.^{47, 53} Some observers are convinced that the mortality from this disease is greater than from infectious (virus III) hepatitis. A poor nutritional state and the existence of other injuries before the onset have been suggested as factors in the higher mortality of some series.⁵² It also seems possible that some strains of virus are more virulent than others.

Incubation Period—The usual incubation period of infectious (virus IH) hepatitis apparently ranges from two to six weeks.^{49, 54, 55} Experimental studies have indicated, however, that certain factors influence the length of this period. Thus, evidence has been obtained that a decrease in the quantity of virus III administered orally to volunteers resulted in a statistically significant prolongation

of the incubation period as compared with that of controls, although in the absence of evidence of attenuation or decrease in the virulence of the virus, the prolongation did not extend beyond thirty-seven days^{20 22} In other experimental studies in which conditions were favorable for attenuation of virus IH before its oral administration to human volunteers, an even greater prolongation of the incubation period was noted, the interval between inoculation and the onset of mild hepatitis being as long as sixty-five days²⁰ It is noteworthy, however, that the prolongation of the incubation period associated with this strain of virus IH was noted only when it apparently was attenuated, as suggested by the mildness of the ensuing disease during which none of the subjects developed overt jaundice or incapacitating symptoms

The incubation period of virus SH hepatitis characteristically is within the range of two to four and one-half months, although the literature suggests an extreme range of one to six months^{3 47, 53} No influence on the interval between inoculation and the onset of acute hepatitis has been demonstrated conclusively in connection with the parenteral administration of small or large quantities of serum or plasma containing virus SH, although it is quite possible that some variation in the wide range of two to four and one-half months may be the result of differences in the quantity administered Although the interval between inoculation with virus SH and the onset of acute hepatitis is long, the occurrence of transient mild symptoms, occasionally associated with laboratory evidences of mild hepatic disturbance and suggesting earlier activity of the virus, has been noted in some instances during the long interval²³

Immunity—The reported epidemiologic data indicate that an attack of infectious (virus IH) hepatitis usually is followed by a relatively permanent resistance to reinfection with the same virus^{3c 5 28 33 48d 57} Studies in human volunteers by Neefe, Stokes, and Gellis^{22 28} and by Havens³³ have confirmed the presence of resistance to reinfection with virus IH during the first year after an infection with this virus Such studies also have provided evidence of an antigenic similarity between a strain of virus IH isolated in Pennsylvania and one isolated in Sicily, volunteers being resistant to infection with the latter after recovery from a previous infection with the former²² Two other observations support this experimental evidence suggesting an antigenic similarity between the United States and Mediterranean strains of virus IH There is considerable evidence to support the belief that the resistance of persons over thirty years of age to virus IH is due, at least in part, to acquired immunity If so, the evidence indicating that the group resistance of United States Army soldiers over thirty years of age to infection with Mediterranean strains of virus IH was greater than that of the younger age groups suggests an

antigenic similarity between the Mediterranean strains and those previously encountered in the United States. The fact that human immune serum (gamma) globulin prepared from plasma obtained in the United States was effective, in doses as small as 0.06 ml per pound, in protecting against both the United States and Mediterranean strains of virus IH also provides suggestive indirect evidence of an antigenic similarity.^{95, 96} Second attacks (not relapses) of infectious (virus IH) hepatitis have been reported with frequencies estimated at 2 to 5 per cent.^{8, 48d, 57} Some of these data, however, were obtained in areas where exposure probably was great and obviously could not be corrected for the unrecognized inapparent nonicteric cases. Gauld^{48d} has suggested, therefore, that the true incidence of second attacks under ordinary circumstances probably is much lower and it seems likely that they are no more frequent than second attacks of measles or mumps. Furthermore, in the absence of specific diagnostic tests it is not possible to assume that the recorded second attacks always have been due to the same virus responsible for a previous attack.

The only data concerning homologous immunity following virus SH hepatitis are those obtained experimentally in volunteers. Oliphant,⁵² and Neefe, Stokes and Gellis^{2, 23} have demonstrated resistance to reinfection with virus SH for periods up to eighteen months after an initial infection with this virus. As these studies did not extend beyond that interval, the duration of such resistance to the homologous virus has not been determined, but it seems probable that it is like that following infections with virus IH, of long duration.

Although infections with both viruses IH and SH apparently are followed by resistance to reinfection with the homologous virus such homologous resistance is not effective against the heterologous virus (IH and SH). The confirmation by experimental studies^{22, 23, 33} of the epidemiological data^{48a, 57} indicating the existence of homologous immunity but an absence of cross immunity appears to provide conclusive evidence of at least antigenic differences between the two viruses. Oliphant⁵² has reported experimental data suggesting a cross immunity between a strain of virus SH and one considered to be a strain of virus IH. His data show, however, that this strain of virus IH injected parenterally into normal volunteers induced hepatitis after an interval of approximately three months the behavior thus being more characteristic of a strain of virus SH than IH. The strain was considered to be one of virus IH on the basis of the history of the case from which it had been isolated. Because designation of a hepatitis virus as a strain of virus IH or SH on the basis of the history of the case is subject to error it seems possible that Oliphant's strain of virus IH actually may have been one of virus SH. Furthermore the ages of Oliphant's subjects used in the cross immunity study were not mentioned, a factor of considerable importance in interpretation of the

results because of the decreased susceptibility of persons over thirty to virus IH. The results of this experimental study thus do not necessarily differ from the experimental results obtained by others,^{22 33} which are supported by the results of epidemiological studies^{48c 57} and indicate a lack of cross immunity.

The increased resistance of groups over thirty years of age to *infectious (virus IH) hepatitis* suggests that this virus may be sufficiently widespread to immunize most of the population by apparent or inapparent infections during the earlier years of life. Experimental evidence of immunization by inapparent infections with this virus has been obtained by Neefe, Gellis and Stokes²². On the other hand, the limited data available suggest that there is no decrease in susceptibility to *virus SH* with increasing age. To speculate on the basis of present knowledge concerning the method of dissemination of this virus, one might postulate that the absence of increased resistance among the older groups might be due to infrequent exposure to this virus during early life. This possibly may be the result of a limited distribution of the virus due to infrequent opportunities for entry into the human host by the parenteral route, the virus apparently being relatively inactive when entry is by other routes. These observations, if correct, are also of considerable importance in the explanation of the different results obtained in the prophylactic use of human immune serum (gamma) globulin in the two types of virus hepatitis.

Methods of Transmission — **INFECTIOUS (VIRUS IH) HEPATITIS** — Before discussing the possible methods of transmission of infectious (virus IH) hepatitis, a brief consideration of the general characteristics of epidemics appears desirable.^{8, 20, 26, 30 48c 49, 50, 55, 56 58, 59, 60, 61 62, 63, 64} Epidemics usually occur under conditions which favor crowding and deterioration of general sanitation and personal hygiene. Such conditions are prevalent in times of war and, in peace time, are encountered most frequently in camps, institutions and within certain family units. Gauld^{48c} states that the typical and most frequently occurring type of epidemic is not explosive in character, but rather runs a leisurely course, taking from three to three and one-half months to spread through a given population. In this type, the epidemic is likely to begin with an initial case followed by single, or sometimes several, additional cases occurring at one to three week intervals. This also is the typical course of outbreaks within families. In addition to this common type of epidemic pattern, at least four epidemics^{20 48c 65, 66} have been reported in which the onset was more explosive and the subsequent course of the epidemic more rapid. This pattern is characteristic of that usually noted with mass infection from a common source, and in these instances the virus apparently was disseminated by contaminated drinking water.

As no host of hepatitis viruses other than man has been established, current theories of the modes of transmission refer to apparently or

inapparently infected humans as the common source of these viruses. The existence of hosts other than man has not, however, been excluded. The different characteristics of certain epidemics of this disease indicate that more than one method of transmission is involved. The pattern of the common type of epidemic has been regarded as indicative of some form of direct or indirect transmission from person to person.^{48c} On the other hand, it seems possible that such a distribution of cases occasionally might result from a common source subject to intermittent contamination with only very small quantities of virus IH or to one, such as drinking water, subjected to procedures which partially, but not completely, eliminate and/or inactivate any virus that may be present.

In some epidemics of this type, *respiratory transmission* has been considered more compatible with the epidemiological observations than any other method^{20 40 50 54 55} and Gauld^{48c} has suggested that the seasonal trend of this disease favors a respiratory means of transmission. On the other hand, the epidemic disease frequently has failed to spread in an apparent form under conditions which should be favorable for respiratory transmission (in hospital wards, etc.)^{2c, 40 63 67} Furthermore, experimental attempts to demonstrate the virus in nasopharyngeal washings obtained from patients during the preicteric and icteric stages of the disease with one possible exception, have been unsuccessful. The experimental studies have not, however, excluded the nasopharynx as a source of the virus during some portion, perhaps very brief, of the incubation period. In addition, the nasopharyngeal washings tested may have been obtained from cases infected by a route other than the respiratory tract, and it is possible that the presence of virus in the nasopharynx may depend on whether or not it was the initial portal of entry. The possibility of the existence of such a factor receives some support from the reports of a high incidence of upper respiratory symptoms during the preicteric phase of the disease in some epidemics and their apparent infrequency in other epidemics. This might account for our failure and perhaps that of others, to demonstrate the virus in nasopharyngeal washings obtained from patients or volunteers in whom the disease had been induced by oral inoculation. Thus respiratory transmission has not been excluded as an important factor in some epidemics, although supporting experimental data are lacking.

Experimental studies have shown conclusively that virus IH may be transmitted by *parenteral infection* (or *oral ingestion*) of *infected blood or its products*. Although transmission by this means is thus possible, it may account for only a minority of the clinically apparent infections. Most of the outbreaks of hepatitis that clearly have been related to the injection of blood or its products have been more characteristic of the type associated with virus SH. Experimental results obtained with strain of virus IH offer a possible explanation for a

compared with virus SH, of apparent virus IH infections transmitted by the parenteral route.²² This strain of virus IH in serum, although highly effective in inducing hepatitis when administered orally to volunteers, was relatively ineffective in inducing the disease when administered parenterally to *normal* persons. In spite of the relative resistance of normal volunteers to this strain of virus IH administered parenterally, those who previously had had hepatitis due to virus SH were highly susceptible to the same parenterally administered virus IH. Furthermore, other strains of virus IH^{8 34} apparently were nearly as effective in inducing the disease in normal persons when administered parenterally as when administered orally. It would appear, therefore, that virus IH may be transmitted by parenteral injection of blood or its products as frequently as or more frequently than virus SH, but the incidence of clinically apparent infections resulting from such transmission may be lower, due, in part, to the relative resistance of normal persons to certain strains of virus IH when entry is by the parenteral route.

Theoretical observations (see "Prevention and Control") concerning the risk of acquiring hepatitis from blood products and concerning some of the factors that may be related to the apparently different results obtained with human immune serum (gamma) globulin in the prophylaxis of virus IH and virus SH hepatitis also afford a possible explanation for the apparently lower incidence of obvious infections of the virus IH type associated with use of pooled blood products. Thus, relatively small pools of adult plasma may contain sufficient specific protective substances to neutralize or inactivate virus IH, whereas, according to the theory, such pools might not contain sufficient specific protective substances to neutralize or inactivate virus SH.

As the high incidence of virus IH hepatitis in recent years thus does not seem to be adequately explained by respiratory transmission or by parenteral entry in infected blood products, other methods of transmission have received increased consideration. Experimental studies have shown conclusively that virus IH frequently is present in the feces of persons with the active disease, regardless of whether entry has been by the oral or parenteral route, and that it is highly effective in inducing the disease in normal persons when it enters by the oral route. The intestinal-oral circuit of the virus thus has much experimental (and epidemiological) evidence to support it as one of the natural mechanisms for its perpetuation and spread from person to person.^{8 20 22 26 48 49 63} On the basis of our present knowledge, therefore, it would appear that a common source of this virus is the feces of infected persons, and that anything subject to direct or indirect contamination with human feces must be considered a potential means of transmission. The resistance of the virus to conditions which inacti-

disinfected water may be one source of occasional sporadic cases or of some small outbreaks of infectious (virus IH) hepatitis which do not conform to the usual pattern of water-borne infections

Transmission of the virus from feces by the other means mentioned, particularly by *personal contact* and *fomites*, appears highly probable and could account for the pattern of the "typical epidemic" as well as could respiratory transmission

Thus, both experimental and epidemiological evidence indicate that the intestinal-oral circuit is one of the important mechanisms involved in the spread of this disease. Respiratory transmission as a cause of some epidemics and sporadic cases remains a strong possibility on the basis of epidemiologic data, but proof of its importance is lacking. Transmission by the parenteral introduction of infected blood or its products may occur, but possibly accounts for only a small proportion of the apparent infections with this virus

HOMOLOGOUS SERUM (VIRUS SH) HEPATITIS—The problems connected with the transmission of homologous serum (virus SH) hepatitis appear to be somewhat different. Conclusive experimental evidence has been obtained that this virus may be present in the blood during the incubation period long before the onset of acute hepatitis, as well as during the active disease. It also seems probable that certain persons may at times carry this agent in the blood stream without ever developing clinical manifestations of acute hepatitis. This is suggested by the fact that donors who have contributed to certain plasma pools which subsequently were shown to contain virus SH frequently have had no history suggestive of previous hepatitis and subsequently have developed no signs of the disease during a prolonged follow-up period. As previously stated, Findlay and Martin³¹ have presented evidence suggesting that this virus was present in the nasopharyngeal secretions of patients in the early stages of the active disease. This, however, has not been confirmed, and epidemiologic data suggest that this virus (SH) seldom is acquired through personal contact alone.^{34, 3} Attempts to demonstrate the presence of virus SH in the feces of patients with the active disease by both oral and parenteral inoculations of volunteers have been unsuccessful.^{22, 23, 30} Finally, the *oral* administration of plasma known to contain one strain of this virus and highly effective in inducing the disease when administered *parenterally*, has failed to induce the disease in volunteers, suggesting that some strains of this agent may be relatively ineffective when entry is by the oral route.²²

The failure to demonstrate this virus consistently in human biological materials other than blood or its products and the apparent ineffectiveness of certain strains when entry is by the oral route have indicated that the principal source of infection with this virus is from *blood or its products* and that transmission occurs most frequently as a result of

the parenteral introduction of such materials. The relatively infrequent opportunities for this type of transmission may be a limiting factor in the distribution of this virus. Such transmission of virus SH (and also virus IH) may result from transfusion of blood, plasma, serum or their products or from their inclusion in biologicals which are administered parenterally for diagnostic, prophylactic or therapeutic purposes. The last mentioned mechanism is dramatically illustrated by the 1942 epidemic among United States Army soldiers injected with yellow fever vaccine (containing human serum) for prophylactic purposes.^{84 85}

Recently it has been suggested that the use of *improperly sterilized syringes and needles* may account for some instances of transmission of the virus.^{4* 43 44 45 46 70 71} Experimental studies have shown that parenterally injected quantities at least as small as 0.1 milliliter of infective serum are sufficient to induce the disease.^{8 12} The resistance of these viruses to procedures which destroy bacteria has already been mentioned. The survival of bacteria in syringes and needles which have been washed, rinsed and passed through disinfecting solutions has been demonstrated, and the survival of the more resistant hepatitis virus under such conditions is even more likely. Subsequent use of such syringes and needles for parenteral injection may suffice to transmit this virus. Recent studies have also suggested that the use of such syringes and needles merely for withdrawal of blood, without the intentional injection of any of the syringe contents, may be sufficient to transmit the virus. Thus, the temporary occurrence of a negative pressure within a vein following release of a tourniquet applied as an aid in the withdrawal of venous blood, apparently is enough to withdraw minute quantities of the needle contents. In addition, when the flow of blood is inadequate during venipuncture, considerable suction frequently is applied intentionally, and the resulting negative pressure easily might draw into the vein small quantities of the contents of the syringe and needle.

Finally in any disease in which the virus is present in the blood and in which minute quantities of blood are sufficient to carry the infectious agent, the possibility of transmission, biological or mechanical, by *biting insects* must be considered. No definite evidence however, of such transmission has been recorded to date.

It is apparent that the recognized methods of transmission of virus SH are all artificial. As no other source or natural method of transmission of virus SH has been definitely established, the origin and natural perpetuation of this virus remain a mystery. The lack of any suitable explanation for its natural perpetuation has led some to question its differentiation from virus IH. The strong evidence indicating a difference in these agents does not, however, justify the assumption that they originally were identical merely because of the lack of an explanation for the natural perpetuation of virus SH. The possibility that

virus SH represents some modification or mutation of virus IH cannot be excluded, although experiences with mutations of other organisms suggest that the general immunological characteristics tend to be preserved. Finally, the possibility that biting insects may play a role in the natural perpetuation of this virus is worthy of consideration.

PATHOLOGY

The previous concept of the pathology of this disease, based on the contention of Virchow⁷³ that the essential lesion is an obstruction of the extrahepatic bile passages due to a mucous plug (which led to the term "catarrhal jaundice") is no longer tenable. During the first world war, Eppinger⁷⁴ revealed the true nature of the lesion of virus hepatitis as an inflammatory process involving the liver parenchyma. The subsequent studies of Roholm and Iversen⁷⁵ and those of Dible, McMichael and Sherlock,⁷⁶ in which the hepatic lesions present at different stages of the disease were investigated by means of liver biopsies obtained from nonfatal cases, contributed much to the understanding of the disease.

Dible and his associates studied the hepatic pathological changes in fifty-six cases of nonfatal acute hepatitis. The group included fourteen cases of so-called epidemic hepatitis, five cases of jaundice following the injection of mumps convalescent serum, two cases of jaundice after the transfusion of serum, and thirty-five cases of delayed jaundice following arsenotherapy (which now is presumed to be a form of virus SH hepatitis in which the agent is transmitted from blood³⁰ by contaminated needles or syringes). The common finding in all cases was an hepatic inflammation of varying intensity and distribution. Regardless of the etiology, one type of case could not be differentiated from another by histologic criteria. (No differences between the changes associated with virus IH hepatitis and those with virus SH hepatitis have been reported to date.) The essential changes consisted of hepatic cell necrosis and autolysis and of leukocytic and histiocytic infiltration. The centers of the lobules showed the first of these changes to the most marked degree, and the periportal spaces had the greatest cellular infiltration. In cases mild from the beginning, or in which the lesion was retrogressing, the periportal cell accumulations predominated. In the more severe cases, hepatic cell necrosis and autolysis were outstanding and the leukocytic and histiocytic infiltration was more widespread. Some specimens exhibited nodular hyperplasia and cirrhotic changes. As a rule, diffuse hepatitis was found to heal completely and rapidly, a process substantiated by the findings of Lucke.⁷⁷ In some patients who had prolonged courses slight fibrosis was noted in the portal zones even after apparent clinical cure. The mechanism of the production of jaundice was thought to involve the disruption of the liver cell columns and their intercellular bile canaliculi, the functional

inadequacy of the damaged cells, and the plugging of the canaliculi with bile thrombi. There was no evidence of bile retention in the interlobular branches of the bile ducts, further demonstrating the intra lobular nature of any obstruction to the outflow of bile that existed.

Fox and his associates⁷⁸ reported similar observations of cases that occurred in Brazil. They occasionally noted, however, the changes of nonobstructive biliary cirrhosis. During the recent war Mallory and his associates made extensive studies on liver biopsy specimens obtained from many cases of nonfatal infectious (virus IH) hepatitis. Additional contributions to the knowledge of this aspect of virus hepatitis are to be anticipated from their as yet unpublished reports.

Lucke⁷⁹ has made a notable study of the pathology of fatal cases of virus hepatitis (a strain of virus SH present in certain lots of yellow fever vaccine appears to have been responsible for most of these). The involvement of the liver was not uniform. Complete destruction of the parenchyma, leaving only skeletal remnants of the lobule, was observed in some areas, whereas in others destruction was incomplete. The destruction apparently affected only the liver cells, the framework and sinusoids remaining unaltered. In and about the areas of destruction an inflammatory cellular reaction was observed. Some of the efferent veins were the site of a marked endophlebitis. In some instances new tissue, which grossly appeared nodular or tumor like, and which microscopically presented an abnormal lobular structure suggested hyperplasia of surviving cells. This tissue was markedly ischemic and overlaid with bile, apparently due to obstruction in the intralobular canaliculi, the extralobular bile ducts appearing normal. The regional lymph nodes near the liver were edematous and often hyperplastic. In the gastrointestinal tract, edema was commonly found and in about 15 per cent of the cases a phlegmonous inflammation, particularly in the cecal region, was observed. The kidney usually showed cholemic nephrosis. In about 15 per cent of the cases one or both of two types of changes were observed in the brain: an acute nonspecific degeneration of ganglion cells or a mild meningo-encephalitis. Hemorrhages frequently were observed, particularly in the lung, intestine, epicardium, endocardium and kidney. Ascites was found in about two-thirds of the cases.

Lucke also studied the structure of the livers of fourteen persons one week to fourteen months after recovery from virus hepatitis, the specimens having become available as a result of unrelated fatal accidents or disease.⁷⁷ The livers in all appeared grossly normal. Microscopically the appearance varied somewhat with the interval elapsing after the time of clinical recovery, but in each instance the integrity of all liver lobules was preserved. In about half of the cases persistent cellular infiltration was noted in the portal triads, but significant scarring was not observed in any. On the basis of these findings Lucke concluded

that complete restoration of the hepatic parenchyma occurred in the nonfatal cases of virus hepatitis in which clinical recovery had been achieved

I have reported the findings in liver biopsy specimens obtained from two volunteers who, after subsidence of the jaundice associated with induced virus IH hepatitis, continued to have mild incapacitating symptoms for eight to ten months (chronic active nonicteric hepatitis)⁸⁰ During the last few months during which the symptoms persisted, most of the commonly used laboratory tests for hepatic disturbance gave normal results The liver biopsies, obtained during the sixth and ninth months after the onset of the disease, showed evidence of mild persistent hepatitis characterized chiefly by leukocytic and histiocytic infiltrations in the periportal spaces and, in one of the cases and to a lesser extent, within the lobules The liver cells appeared relatively normal

It is apparent that a few of the patients with virus hepatitis develop a chronic form of the disease The findings in some such cases in which the outcome was fatal are included in the series of Lucke mentioned previously The outcome, in terms of pathological anatomy, of those cases in which the disease persists in a chronic form for long periods has not been definitely established It has been suggested that in some of these cases portal cirrhosis may develop, but this has not been proved Likewise, it has been suggested that some of the cases of hypertrophic biliary cirrhosis actually may be a chronic form of virus hepatitis Watson and Hoffbauer²⁵ recently have reviewed the problem of prolonged hepatitis and its relationship to the development of cirrhosis Cases considered to illustrate the transition from hepatitis to cirrhosis are presented In these cases, the findings were similar to those of hypertrophic biliary cirrhosis (Hanot) They suggest the term "cholangiolitic cirrhosis" as more appropriate and distinctive and differentiate it from the hypertrophic fatty liver which represents an intermediate stage between the fatty liver and the atrophic cirrhosis of chronic alcoholics or other conditions associated with dietary deficiency They also suggest that the end stages of the cholangiolitic cirrhosis following prolonged hepatitis may be indistinguishable anatomically from ordinary atrophic or portal cirrhosis

CLINICAL MANIFESTATIONS OF VIRUS HEPATITIS

The symptoms, physical and laboratory findings and the diagnosis of virus hepatitis have been described fully in recent reports^{3c 5 9 22 23, 47 50 53 56 63 80 81 82, 83 84 85} and do not warrant detailed consideration here Certain clinical aspects, however, are worthy of further emphasis Experience during the recent war has shown that virus hepatitis is not the benign disease it has usually been considered on the basis of experience with "catarrhal jaundice" in children In adults, the period

of disability averages from six to eight weeks^{82, 85} The disease carries a small but significant mortality which may be increased by improper management. Of considerable importance is the fact that the potentially fatal cases cannot be predicted on the basis of the severity of previous symptoms Those with the mildest symptoms, even without jaundice, may suddenly deteriorate and die within twenty four to forty-eight hours Death may occur during the first week of the disease or only after weeks or months of illness Because of the unpredictability of the disease and the apparently beneficial effects of proper treatment, it appears that all cases, regardless of the severity, should be treated as potentially fatal cases even though the actual mortality is low The development of mental symptoms other than simple depression, pernicious vomiting and ascites during the course of hepatitis may afford the first clinical suggestion of an impending fatal outcome⁷⁹

The manifestations of the typical case of "infectious (virus IH) hepatitis" do not differ from those familiar to all from the textbook descriptions of so-called "catarrhal jaundice" with its preicteric, icteric and convalescent stages Homologous serum (virus SH) hepatitis is clinically indistinguishable from infectious (virus IH) hepatitis although fairly consistent differences in the types of onset have been noted Thus, the onset of the former is likely to be rather insidious with a slowly progressive increase in the symptoms, and the temperature frequently is normal throughout the course of the disease The picture frequently has no resemblance to an infectious process In contrast, the onset of virus IH hepatitis, regardless of whether the route of entry is oral or parenteral, tends to be abrupt with fever and general symptoms that are common to the onset of a variety of acute febrile illnesses Fever also appears to be common in the milder nonicteric cases These differences are apparent only during the first few days of the respective diseases, thereafter the course of virus IH hepatitis and virus SH hepatitis are entirely similar and are characterized more by the manifestations of liver injury than by those of an infection. Unfortunately, the variability of the disease in individual cases does not permit differentiation of virus IH hepatitis from virus SH hepatitis on the basis of the type of onset

That virus hepatitis may occur in a form *without overt jaundice* has been unequivocally established^{70 72, 73, 75 48 63 80 81} Recognition of this form of the disease is essential because of its epidemiological importance and because inadequate treatment may lead to prolonged illness, relapses and occasionally a chronic form of the disease The incidence of hepatitis without jaundice probably varies with age, management, the previous general condition of the patient and the virulence of the virus In different epidemics the estimated incidence has varied from 28 to 80 per cent of the total number of apparent infections

Relapse or recrudescence resulting in prolongation of the illness (and

occasionally death) is not infrequent^{80 82, 83 85} The exact incidence has not been established and may vary with the strain of virus, the resistance and condition (nutritional and otherwise) of the patient and the type of management Hoagland and Shank⁸⁵ reported an incidence of relapse or recrudescence of 18.5 per cent in 200 well treated cases, the recrudescence in 82 per cent following the resumption of physical activity associated with the first grant of liberty or temporary hospital discharge. An average of twenty days' additional hospitalization was required for these cases. Mild relapses resulting in transient to more prolonged periods (up to one year) of partial disability were observed in approximately 15 per cent of volunteers who acquired virus hepatitis under favorable experimental conditions⁸⁰ Relapse thus may occur in spite of the method of management, but an increased incidence has been related to premature resumption of activity, intercurrent infection, tissue trauma, excessive consumption of alcohol and inadequate dietary management⁸³

Although most patients with virus hepatitis apparently recover completely from the disease within eight weeks, an estimated 5 to 20 per cent, probably depending on the conditions mentioned before, do not recover completely within a period of four months. Barker, Capps, and Allen⁸³ have applied the term "*chronic hepatitis*, without implication regarding the nature of the pathologic process or the eventual prognosis," to this group of patients with evidence of active hepatitis that has persisted four or more months after the onset. The group includes some who have had well defined relapses as well as others in whom the activity of the disease has remained stationary, has increased, or has slowly decreased. The cause of the persistence of the disease and its outcome in those of this group who do not have a fatal termination has not been established. Whether or not it is due to continued virus activity and whether the virus is present in the blood and excreta of these cases are unsettled problems of crucial importance.

Published reports suggest that *several clinical types of chronic hepatitis may occur*^{80 82 83 86} The picture may consist of (1) incapacitating symptoms, physical signs including overt jaundice and laboratory evidence of hepatic disturbance (chronic active hepatitis with jaundice), (2) incapacitating symptoms and laboratory evidence of hepatic disturbance, with or without physical signs, and without overt jaundice (chronic active hepatitis without jaundice), (3) incapacitating symptoms without physical signs or laboratory evidence of hepatic disturbance (chronic active hepatitis without jaundice, probably frequently confused with psychoneurosis), (4) laboratory evidences of persistent hepatic disturbance without symptoms or physical signs (chronic inactive hepatitis without jaundice—Barker et al), and (5) possibly a form with persistent mild jaundice but without symptoms, physical signs or laboratory evidence of hepatic disturbance other than hyper-

bilirubinemia (chronic inactive hepatitis with jaundice?) * Because of the high incidence of virus hepatitis during recent years, the existence of many cases of chronic hepatitis appears highly probable. Recognition of such a syndrome and its clinical manifestations is therefore of importance if errors in diagnosis are to be avoided. Such cases may also prove to be of epidemiological importance.

DIAGNOSIS OF VIRUS HEPATITIS

As no specific diagnostic test for any of the types of virus hepatitis has been developed, the diagnosis is based on clinical and epidemiological grounds, and some assistance is derived from the fairly consistent, though nonspecific, responses of certain laboratory procedures. The general diagnostic features of virus hepatitis have been adequately described in recent reports. Certain aspects, however, seem worthy of additional emphasis or amplification. The initial problem is the establishment of the diagnosis as one of the types of virus hepatitis. The various conditions from which this disease must be differentiated depend on the stage of the disease. During the preicteric stage or in hepatitis without jaundice, the picture may simulate that of any acute febrile illness. Tenderness in the hepatic area and other evidences of hepatic disturbance (bromsulfalein retention, bilirubinuria and urobilinogenuria) frequently are found within twenty-four to seventy-two hours after the onset. Such indications of hepatic disturbance occurring promptly after the onset appear to be the most suggestive evidences of hepatitis at this stage of the disease. The frequent occurrence of mild to severe abdominal pain, often associated with marked tenderness and sometimes muscular spasm, at the onset of hepatitis deserves emphasis because of its frequent confusion with the similar manifestations of an "acute surgical abdomen." Of equal importance, particularly in the older age groups, is the recognition of the insidious type of onset, in which the chief manifestation is a relatively silent and progressive jaundice. This is not uncommon with homologous serum (virus SH) hepatitis and may easily be confused with malignant obstructions of the biliary tract. Because of the increased prevalence of virus SH hepatitis and because, in civilian medicine, transfusions of blood or plasma are given most frequently to persons of the older age groups, virus SH hepatitis now must be recognized as one of the common causes of jaundice in the older age groups. The fact that loss of weight, sometimes marked, is almost the rule in virus hepatitis is also worthy of additional emphasis.

Properly selected hepatic tests are of considerable value as aids in the diagnosis and management of virus hepatitis. They frequently afford the only evidence of hepatic disturbance in the preicteric stage.

* Conclusive evidence that this represents one of the chronic forms or residual effects of virus hepatitis is lacking.

of the disease and in some of the cases of hepatitis without jaundice, they are also particularly helpful in the evaluation of the completeness of recovery during the posticteric or convalescent stage. They are useful in the icteric stage as aids in the differential diagnosis between hepatic and extrahepatic obstructive jaundice and as a means of following the course of the disease. The information obtained, however, depends to a large extent on the tests used. In a recent analysis of the results obtained in this laboratory⁸⁷ with a group of hepatic tests performed at frequent intervals throughout the course of infectious (virus IH) hepatitis, certain tests that were among the most prompt and consistent indicators of the initial hepatic disturbance during the preicteric stage often were found to be of little value in detecting persistent hepatic disturbance during the posticteric stage of the disease. The variability of response to individual tests with the stage of the disease and the individual patient indicated that a group of tests composed of the total and I' serum bilirubin, urine bilirubin and urobilinogen, cephalin cholesterol flocculation, thymol (turbidity and flocculation), and brom-sulfalein procedures constituted the most reliable *minimum* group of tests for detection of the mild hepatic disturbance associated with certain stages and types of virus hepatitis. During the icteric stage, serial determinations of the serum albumin and of the serum total and esterified cholesterol concentrations offered additional valuable information concerning the severity and course of the disease. Serum alkaline phosphatase was of little value in the study of virus hepatitis except to differentiate it from primarily obstructive types of jaundice when a normal or only slightly elevated alkaline phosphatase in a deeply jaundiced patient favored a hepatic type of jaundice.

Although the literature contains no reference to any difference between the responses to the various hepatic tests in infectious (virus IH) hepatitis and homologous serum (virus SH) hepatitis, recent studies in this laboratory have suggested that the responses to the thymol and colloidal gold tests may be somewhat different in the two types of hepatitis.⁸⁸ In two small but closely comparable groups of patients with induced virus IH hepatitis and induced virus SH hepatitis, respectively, the responses to the serum colloidal gold and thymol (turbidity and flocculation) tests were less in degree and duration in the virus SH hepatitis group than in the other group, whereas the responses to the cephalin cholesterol flocculation test were maximal in both groups. Thus in four of the six patients with virus SH hepatitis (with jaundice), normal or only weakly positive responses to colloidal gold and thymol tests were obtained throughout the disease. The observed differences in response between these two groups were statistically significant. Whether or not this will prove to be a frequent finding in virus SH hepatitis remains to be determined. However, as strongly positive responses at some stage of the disease to these two

tests have been the rule in most cases of virus IH hepatitis, the finding that normal or weakly positive responses may be encountered in some cases of virus SH hepatitis appears to be of clinical importance in showing that this does not constitute evidence against the diagnosis of hepatitis

In this laboratory^{23, 25} the bilirubin excretion test has failed to give the consistent responses in normal persons indicated by previous reports.²⁶ When the test was performed at frequent intervals over a period of time by the usual technic on each of a group of apparently normal healthy young men without history or existing evidence of hepatic disturbance widely varying responses were obtained both in the group and the individuals. It would appear that abnormal results, based on the usual criteria, with this test *alone* should be interpreted with caution as evidence of latent liver disease in persons recovered from virus hepatitis, particularly those who have normal fasting serum bilirubin concentrations and who present no other evidence of hepatic disturbance detectable by clinical or laboratory means

TREATMENT OF VIRUS HEPATITIS

The general management of virus hepatitis and the special measures required for certain cases have been considered in the recent reports of Barker, Capps and Allen,^{22, 23} of Hughes,²⁹ Hoagland and Shank,²⁵ and others.²⁶ The present discussion, therefore will refer only to the data providing a rational basis for the current principles of treatment.

Rest—No specific treatment for virus hepatitis has been developed. Nevertheless, the beneficial effect of nonspecific measures has been adequately demonstrated. The results of the studies of Barker and associates Hoagland and Shank, and Hughes led them to the definite conclusion that physical activity during active hepatitis has an adverse effect on the course of the disease and that marked restriction of physical activity (by complete or almost complete bed rest) until convalescence is well established results in a significant shortening of the course of the disease and a decrease in the incidence of relapses and chronic cases. The data of these investigators appear to provide adequate evidence that restriction of physical activity is one of the most important therapeutic measures available for this disease. The length of time during which such restriction should be recommended varies with the individual case and always is difficult to estimate.

Because the available data suggest that resumption of unrestricted physical activity while the process is still active as it sometimes may be after symptomatic recovery and disappearance of jaundice, leads to prolongation of the period of partial disability and to an increased incidence of prolonged illness the decision obviously is important

and can be made reliably only with the aid of certain laboratory procedures. Barker and his co-workers have found the following criteria, used successfully in the Mediterranean Theater, helpful in making this decision: (1) a three week minimum period of bed rest, (2) absence of liver tenderness and hepatomegaly, absence of symptoms, particularly lassitude and anorexia, (3) normal concentration of total serum bilirubin (or icterus index) and negative prompt direct qualitative Van den Bergh reaction, (4) normal or only slight impairment of bromsulfalein excretion, (5) a negative cephalin cholesterol flocculation test and normal serum alkaline phosphatase were considered desirable but not essential. Studies here have indicated that two additional laboratory procedures, the serum thymol (turbidity and flocculation) test and the I' serum bilirubin reading, are helpful in the evaluation of the completeness of recovery.⁸⁷ In some instances these tests provided evidence of persistent hepatic disturbance that was not revealed by those included in the criteria mentioned. In addition, if weight loss has occurred, evidence of increase in weight is desirable before resumption of activity.

When physical activity is permitted, it should be increased gradually, and, if possible, its effect should be checked at intervals by repetition of the laboratory procedures mentioned. In those patients who continue to have clinical or laboratory evidence of persistent mild disturbance for a long period, a trial of the effect of gradually increasing physical activity is warranted. If this does not result in aggravation of the laboratory findings or clinical manifestations, a gradual return to normal physical activity is usually tolerated. If symptomatic or laboratory evidence indicates an adverse effect, it appears judicious to restrict activity for an additional period of time. Barker and his co-workers have emphasized the importance of persistence or recurrence of tenderness and enlargement of the liver as an index of incomplete recovery or recurrent activity. These findings, however, at times may be absent in patients with other evidences of persistent or recurrent active hepatitis and, in fact, occasionally may be absent throughout the disease. Furthermore, as tenderness is subjective, it alone is not reliable evidence of persistent activity in all patients.

Dietary Therapy—The only other therapeutic measure generally considered of basic importance in the treatment of virus hepatitis is the provision of a nutritionally adequate diet. The composition of the recommended diet is based on the results of experiments in animals which have shown that certain dietary factors are influential in increasing or decreasing the susceptibility of the liver to injury and in hastening or diminishing the rate of repair of the previously damaged liver.^{90, 91} Furthermore, it has been possible to induce hepatic necrosis and cirrhosis (similar to the portal cirrhosis of man) consistently in rats simply by the prolonged administration of a diet qualitatively

or quantitatively deficient in certain proteins⁹¹ The addition of the essential amino acid methionine alone or of the combination of choline plus cystine to such diets has prevented these changes, or, if they are already present, has accelerated repair

Chiefly on the basis of such data and on the evidence which is rapidly accumulating on the beneficial effect of proper dietary treatment in some cases of portal cirrhosis and in other types of hepatic disease, special dietary measures are considered desirable in the treatment of any type of liver disease. Opinions concerning the added beneficial effect of special dietary measures and supplements over the ordinary diet in virus hepatitis have been divided. The great variability in the severity and duration of this disease makes evaluation of the results of any therapeutic measures particularly difficult. Thus some have reported beneficial effects from diets high in protein and carbohydrate and low in fat, whereas others¹⁰³ have failed to observe any apparent influence on the course of the disease associated with such diets It appears probable that one factor governing the result, particularly in a disease of relatively short duration, is the nutritional state of the patient before the onset of the disease.

Barker Capps, and Allen⁸² and Hughes⁸⁰ are convinced that a high caloric, high protein high carbohydrate, low fat intake by hepatitis patients (many of whom probably had not had nutritionally adequate diets before the onset of the illness) resulted in a decrease in the severity and duration of the disease and a lower incidence of prolonged convalescence as compared with that of a control group who received the ordinary hospital diet. More immediate effects were improved morale and more rapid gain in strength and weight. These and the nonspecific animal experimental data appear to support the value of a diet high in total calories, protein and carbohydrate in the treatment of hepatitis

Recent observations by Hoagland, Labby Kunkel and Shank,⁹² who have kindly permitted reference to their as yet unpublished data, have indicated that marked restriction of fat intake may not be necessary when such a diet is provided. In fact, no harmful effects were observed from a diet that was relatively high in fat (approximately 150 gm; principally from milk, cream, butter and eggs) in patients whose protein intake was correspondingly high. The inclusion of a relatively high fat content simplified the maintenance of an adequate caloric intake, and the patients lost less weight during the acute stage of the disease and gained weight more rapidly during the convalescent stage than did control patients on a diet similar except for a low fat content A more rapid decrease in the degree of bromsulphalein retention also was observed in the patients with a high fat, high protein intake They emphasize the importance of the type of fat to be included and refer to the experimental work of Stetten and Salgado indicating the influence of the length of fatty acid chains of the dietary fat on the severity of fatty change in the liver of animals deficient in choline⁹³ Thus the inclusion of at least moderate amounts of "dairy" fats in the hepatitis diet appears desirable, provided a high protein and high carbohydrate intake can be maintained

Data on the value of *dietary supplements* such as methionine and choline plus cystine in hepatitis are conflicting, but in general suggest that these substances afford no additional beneficial effect over a high protein, high carbohydrate^{85, 94} diet. But such diets already contain quantities of these substances that probably are adequate, and an additional beneficial effect hardly would be expected. Another limitation on the validity of some of the reported data concerning the value of such substances is the fact that, in the animal studies,⁹¹ beneficial effects were observed only after prolonged administration, whereas in some of the studies on hepatitis, the substances were given for only short periods.^{85, 91} For these reasons it does not seem justifiable to discontinue completely the therapeutic trials of methionine or cystine plus choline on the basis of the studies reported to date. A reasonable attitude concerning the use of methionine or of cystine plus choline in the treatment of hepatitis would appear to be as follows: (1) Their routine use does not seem warranted in patients whose nutritional status before the onset of hepatitis was good and who are able to take a high protein, high carbohydrate, high caloric diet within a few days of the onset of hepatitis. (2) Further trials are warranted in patients in poor nutritional status before the onset, in those with alarming symptoms, and in those who are not able to consume the recommended diet within a few days of the onset.

PREVENTION AND CONTROL

Prevention of Transmission from Individual Active Cases—In the individual case, virus IH hepatitis frequently cannot be distinguished from virus SH hepatitis with certainty. The same general measures are thus applicable. Attempts to prevent direct or indirect transmission of the virus from feces, using the sanitary and hygienic measures employed in the control of enteric infections, such as bacillary dysentery and typhoid fever, are indicated. Although the interval during which the feces contain the virus is uncertain, such excreta tentatively should be regarded as potentially infectious for at least a month after the onset. Prevention of transmission by blood is also warranted. This should be possible by adequate cleansing and sterilization (boiling for fifteen to thirty minutes or autoclaving) of all syringes and needles before and after each use, whether for intravenous injections or withdrawals or for other parenteral administrations. Obviously blood from such cases should not be administered to others. The possible transmission by needles used for multiple finger punctures in blood counts should be considered and avoided by adequate sterilization between patients. Specimens of blood, feces and urine from hepatitis patients should be protected from flies and other insects, and those sent to laboratories for analysis should be marked as potentially infectious. Although there is no direct evidence indicating

the necessity of vigorous application of the measures generally used for prevention of respiratory transmission, reasonable precautions should be taken.

General Prevention and Control of Infectious (Virus IH) Hepatitis—Prevention of fecal contamination of drinking water, food and milk seems important. The resistance of this virus to procedures which eliminate bacteria suggests that more stringent disinfecting measures than are often applied, particularly in respect to drinking water may be necessary. The desirability of adequate general sanitary measures and personal hygiene are obvious.

No method of *active* immunization has been developed. Recent data²² indicate, however that this may be a future possibility if methods of isolation and propagation of the virus can be developed.

An effective method of *passive* protection against virus IH hepatitis has become available as a result of the finding²³ which has been adequately confirmed,²⁴ that the intramuscular administration of human immune serum (gamma) globulin to exposed persons during the incubation period, before the onset of symptoms afforded complete or almost complete protection. Such gamma globulin is thus indicated as a preventive measure in the presence of a spreading epidemic. The present limited supply makes its routine use in persons exposed to sporadic cases impossible. Its use in exposed pregnant women and persons with other conditions in which any additional illness might be disastrous should, however be considered.

The protective properties of human immune serum (gamma) globulin in virus IH hepatitis suggest that adult serums frequently contain substances capable of neutralizing or inactivating this virus. This may explain, in part, the apparent infrequency of outbreaks of this type of hepatitis after the use of pooled plasma, as compared with the frequency of those due to virus SH.

General Prevention and Control of Virus SH Hepatitis—The lack of a method of demonstrating the presence of virus SH in blood or its products, other than by human inoculation, is the greatest obstacle to the prevention of this disease. Exclusion of persons who have a history of jaundice as blood donors may be of some value. Some persons who might present themselves as blood donors during the incubation period or just at the onset of hepatitis possibly could be detected if a group of hepatic tests were conducted routinely. Unfortunately this is not practical at most blood stations. A single simple test, such as the modified methylene blue²⁷ or modified Harrison spot tests²⁸ for urine bilirubin, could be done routinely at blood stations before a donor is accepted and probably is advisable. The use of the simple methylene blue procedure at certain blood-collecting depots of the United States Army in the Mediterranean Theater of Operations served to exclude a small number of soldiers who unknowingly came

in to donate blood just before the onset of hepatitis⁹⁹ As yet, however, there is no method of excluding as blood donors those who may carry the virus without symptoms or evidence of hepatic disturbance Likewise, no generally applicable method of inactivation of the virus in collected blood or plasma has been developed that does not also render these substances unsatisfactory or unfit for use Nevertheless, a practical method of inactivation of virus SH in human serum albumin solutions without making them unsatisfactory for use¹⁰⁰ has been developed by stabilizing them with acetyl tryptophane and sodium caprylate and heating for ten hours at 60° C The effectiveness of shorter periods of heating at this temperature or for the same period at lower temperatures was not determined

Because no practical means of recognizing infected blood, plasma or serum (or biologicals containing infected blood products) is as yet available, the use of such materials carries a small but definite risk of hepatitis As it seems reasonable that the process of pooling plasma or serum would increase the chances of including an infected sample, the risk of hepatitis would appear to be less with single units of plasma or whole blood Possibly, however, the risk with pooled preparations may depend on the number of different samples included in the pool

Thus most of the blood pools that have been associated with hepatitis have been relatively small, including samples from less than fifty donors Yet the extensive use of human immune serum (gamma) globulin, prepared from large plasma pools composed of several thousands of samples, in the prophylaxis of measles apparently has not induced hepatitis⁹⁵ As certain other viruses in plasma which does not contain their specific antibodies have survived the process of plasma fractionation and have been demonstrated in the various plasma fractions,¹⁰¹ some instances of hepatitis might be expected in any extensive use of the various products of plasma fractionation if the risk of including a hepatitis virus increased progressively with the number of specimens included in the original pool That this apparently has not been so suggests that some specific neutralizing factor may be present in the large plasma pools that is not present, or at least not in sufficient quantity to be protective, in smaller pools This could be explained on the basis that the number of persons who have been immunized against virus SH as a result of inapparent or apparent infections may be small, possibly due to a limited distribution of this virus If so, the chances of including enough plasma with neutralizing properties in the smaller pools also would be small, whereas in the large pools of several thousand samples a number of specimens with neutralizing properties might be included In the case of virus IH, which probably is more widely distributed, the chance of including neutralizing substances may increase more rapidly with the size of the pool Thus even small pools might contain enough substances to neutralize or inactivate the virus This might account for the fact that most outbreaks of hepatitis attributed to the use of pooled plasma have had the characteristics of virus SH rather than virus IH On the basis of such a theory, the risk of including a hepatitis virus may increase progressively with the size of the pool, but after a certain point the risk of acquiring hepatitis may be decreased by the inclusion of increasing quantities of protective substances

These theoretical observations are of interest in connection with the variable results obtained to date with the prophylactic use of gamma globulin against virus SH hepatitis,¹⁰² its consistent effectiveness to date in virus IH hepatitis already having been mentioned. Although a single intramuscular injection of 10 milliliters of gamma globulin in battle casualties who have had transfusions apparently has not been effective in decreasing the incidence of virus SH hepatitis a significant prolongation of the incubation period has been observed.^{102a} When two intramuscular injections of gamma globulin (10 milliliters each) were given one month apart, a significant decrease in the incidence of hepatitis in battle casualties was observed.^{102c} In an experimental study in volunteers,^{102d} mixture of 1 cc of gamma globulin with 2 cc. of infective plasma (virus SH) before injection or the simultaneous injection at separate sites of 10 milliliters of gamma globulin and 2 milliliters of infective plasma did not prevent the disease or prolong the incubation period. The findings suggested that the globulin had no effect under these circumstances. It seems possible that these varying results may be explained in part by the theoretical observations mentioned previously, namely, a relatively low concentration of neutralizing substances effective against virus SH in the gamma globulin preparations used. Thus in a pool of several thousands of samples of plasma, sufficient neutralizing substances might be present to inactivate any hepatitis virus in that pool. Likewise two 10 milliliter doses of gamma globulin may have provided sufficient neutralizing substances to neutralize or inactivate virus SH in infected persons whereas only one 10 milliliter dose may have provided enough substances to delay the onset but not to neutralize all the virus. In the experimental study on volunteers the quantity of globulin, particularly if the concentration of neutralizing substances was low, may have been inadequate to neutralize the quantity of virus present. Thus the inconsistent results obtained to date with gamma globulin in the prophylaxis of virus SH hepatitis do not necessarily indicate that neutralizing substances are absent. Further studies employing larger or multiple doses at different stages during the incubation period are obviously indicated before this question can be settled.

While awaiting the development of some method for control of this virus in plasma, it would seem judicious, in contemplating the use of blood, plasma or substances containing blood products, to weigh the risk of hepatitis against the indication for the use of such substances. The indication obviously will frequently outweigh the risk of hepatitis but the not infrequent use of transfusions of blood or plasma without a definite indication appears inadvisable.

SUMMARY

Some of the data concerning the etiology, epidemiology, pathology, clinical manifestations, diagnosis, treatment, prevention and control of "virus hepatitis" (infectious hepatitis, homologous serum hepatitis, etc.) provided by the numerous and extensive investigations of recent years have been assembled. An attempt has been made to correlate these data in an effort to evaluate and perhaps to clarify, to some extent, the existing knowledge.

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THE APPLICABILITY OF LIVER FUNCTION TESTS IN JAUNDICE OF ACUTE ORIGIN

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THE many contributions dealing with liver function studies during recent years have largely been concentrated on the elaboration and evaluation of individual tests or on surveys of case groups in which various combinations of tests had been applied. At times there has been a tendency to hover over a single test perhaps too closely to recognize its limited field of application, at other times the attempt to secure a wide panorama has resulted in withdrawal to such a distance that technical variations in the hands of individual workers could not be appraised.

To some it may seem that the endeavor to approach the subject of liver function studies has too often been marked by the frequency with which authors have invoked a semi-apologetic preface, dwelling upon the multiplicity and relative dissociation of hepatic functions, the coincidental processes of hepatic cellular degeneration and repair, the reserve capacity of the liver and its remarkable power of regeneration, and finally reaching the obvious conclusion that no single test is adequate to represent the total functional status of the organ at a given time. These limitations, however obvious, require frequent repetition, if only as reminders that this mass of multifunctional, largely interdependent cells within a common capsule is highly dynamic and must be so studied. Furthermore, the value of any laboratory procedure is circumscribed by the variability of technic from one institution to another, the laudable ambition of many investigators to superimpose minor modifications on original procedures, and the vagaries of all concerned—physicians, nurses, patients and technicians alike—in the business of securing specimens for study.

Despite these problems and hazards, liver function studies have come to represent a sound source of information, diagnostic, prognostic, or both, provided their specific spheres of value are understood. Inasmuch as data concerning individual and comparative studies have been clearly elaborated one or many times, at first glance there would seem to be no reasonable justification for this contribution. However, experience in both civilian and military medicine has convinced me that liver function studies in general are the subject of a widespread

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distrust and are frequently misapplied and erroneously interpreted. Far too often for example, a normal galactose tolerance test in a non jaundiced individual has led to an assumption of normal liver function, just as a slightly elevated retention of bromsulfalein has resulted in the false incrimination of the liver in a patient with cardiovascular inadequacy

It is believed, therefore, that the attempt should be made to survey the field of liver function tests in order to outline broadly their specific fields of applicability and, because of the inherently dynamic nature of hepatic activity, to stress the need for serialization of studies. In recent years, particularly in the armed forces, the high incidence of all types of jaundice has brought the problem into increased prominence, particularly with regard to the occurrence of jaundice of acute origin

The phrase, jaundice of acute origin, is promptly recognizable as a loose term, embodying both closely circumscribed entities and ill defined syndromes. In both groups there remains much to be learned regarding etiology, infectivity and mode of transmission, as well as diagnosis and therapy. Their only common features are the pathological involvement of the liver, the occurrence (with one exception) of jaundice, and a phase, at least initially of acuteness. Their prevalence and their frequent inclination toward chronicity or residual damage, often without relation to the severity of the acute phase, render them formidable. Any attempt at classification at this time is certainly subject to change in the light of new and dawning concepts. At this time we may include, purely for the purpose of this discussion acute toxic degenerative hepatitis, leptospirosis so-called hepatitis without jaundice, chemical hepatitis, acute and subacute yellow atrophy and, if it exists as a separate entity catarrhal jaundice.

A SERIALIZED SYSTEM OF STUDY

The laboratory observation of jaundice of acute origin may be considered as falling into three phases concerned with (1) diagnosis (2) immediate prognosis and (3) remote prognosis. In other words, we seek the answer to the questions of (1) whether jaundice is present and the nature of its cause, (2) the patient's status throughout the acute period of illness, and (3) his more remote prognosis as regards cure and residual damage or chronicity

It is obvious that such a grouping is based partially on time elements partially on elements of significant factual information. Because of the need, in many cases, for an immediate appraisal of the patient's status as regards either prophylactic or definitive therapy much of the data to be obtained from studies of immediate prognosis must be secured concurrently with data from those of diagnostic

import It must be borne in mind that while too great a value cannot be placed on such studies, the constantly maintained clinical observation of the jaundiced patient remains the major factor in his care, this is true equally during the acute period of illness and during the convalescent or chronic phases

The diagnostic studies represent the attempt to disclose the impending or actual presence of jaundice and to discover, whenever possible, its etiologic identity The immediate prognostic tests disclose, during the acute illness, the effect on the patient of the interaction between the disease agent and the responding mechanisms and require frequent serialization to represent truly the dynamic changes which occur during the period of acute illness The remote prognostic studies, performed after regression of the acute phase, serve to guide the assessment of probability of recurrence, of tendency toward chronicity, and of the status of residual damage and repair

1 Diagnostic Studies.

- (a) Van den Bergh Reaction
- (b) Icterus Index Test
- (c) Galactose Tolerance Test
- (d) Methylene Blue Test
- (e) Flat Plate of Abdomen
- (f) Leptospira Antibody Titer Determination

While the great majority of cases of jaundice are readily detectable on inspection in good light, the accurate determination of bilirubinemia may be necessary in very early cases, cases in which icterus is never deep and cases occurring in the presence of atabrine discoloration Such a determination is quickly reached by an initial van den Bergh or icterus index reading which, in addition, serves as a starting point for observation of the flow and ebb of icterus throughout the course of the disease

Little need be said regarding the *icterus index* as representing a simple procedure for the rough quantitative estimation of serum bilirubin, it is easily performed and, provided there is no great degree of lipemic opalescence, hemolysis, carotinemia or luteinemia, it is sufficiently accurate for practical purposes The potential sources of error are largely eliminated by careful observance of technic and by the patient's total abstinence from food during a twelve hour overnight fast Further refinement of procedure is readily secured, when desired, by the acetone dilution method, but the 50 to 60 per cent lowering of readings by this modification must be borne in mind when comparative studies are made

As a check on this method of recording bilirubinemia, it is well to obtain a truly chemical test as exemplified by the *van den Bergh reaction* This specific estimation of bilirubinemia obviates possible physical sources of error but has the disadvantage of requiring more

time and care in performance and, in the study of prompt reacting bilirubin, equipment not universally obtainable. However, in the initial study of a case, it is extremely valuable in verifying low grade states of icterus, in disclosing the presence of latent, or subclinical jaundice, and as an aid in directing attention to the occasional case of hemolytic jaundice. This last is particularly true when the Lepehne modification of the qualitative reaction is employed, just as the accuracy of the quantitative test is heightened by the use of the Thannhauser and Anderson or more recently, the Watson^{1 2 3} modifications.

Originally proposed by Franke⁴ in 1931 the *methylene blue test* has lately come into prominence particularly as a result of work by Gellis⁵ and others within the past two years. A remarkably simple procedure, it apparently not only gives information as to the presence of acute hepatic degenerative disease but may become positive from one to six days before jaundice is observed clinically and a shorter period before hyperbilirubinemia may be detected. Further corroborative evidence is necessary and studies are widely in progress those to date are exceedingly promising. While the study of urobilinogen as far back as 1925 by Wallace and Diamond⁶ and the recent quantitative estimation by Watson and his co-workers⁷ appear to present parallel information, a reading obtained simply from the mere drop by drop addition of a 0.2 per cent aqueous solution of methylene blue chloride to 5 cc. of a prebreakfast specimen of urine has the great advantage of economy of time, material and availability. The problem of the physical, chemical or combined nature of the reaction is yet unsettled, but the present theory inclines largely toward the physical as being preponderant.

Many definitive studies have been attempted to establish the differential diagnosis of jaundice of acute origin as distinguished from that of a chronic nature. Many who have used the *galactose tolerance test* over a long period of time have found it highly satisfactory,^{8 9} and at least a portion of the criticism leveled against it has been the result of use of widely varied modifications, failure to give full instructions to the patient in the collection of specimens, the use of the test in non-jaundiced patients, or failure to serialize the test in order to obtain positive readings at the ebb of carbohydrate functional integrity. Glycogenolysis is not a specialized job for a limited highly trained cell of the liver; it is the common labor for which every polygonal cell has a great capacity far beyond that which it is ordinarily called upon to perform. It is obvious, therefore, that only a diffuse process affecting the great masses of hepatic cells is apt to produce notable and measurable alteration of carbohydrate function. For all practical purposes it may be said that such a diffuse involvement is produced exclusively by acute toxic, degenerative or inflammatory processes such as are included in the group here termed jaundice of acute origin.

It follows, therefore, that tests of carbohydrate function, the galactose test in particular, are applicable only to cases of jaundice which are due to acute diffuse processes that have become spotlighted by the failure to maintain a specified efficiency of carbohydrate metabolism. A positive oral galactose tolerance test, one in which a minimum of 30 gm of galactose is excreted in a five hour collection of urine following the ingestion of 40 gm of the test sugar, makes for a definite diagnosis of acute diffuse liver disease and will occur almost invariably during the course of jaundice of acute origin.

It must be remembered, however, that such a positive test may not appear coincidentally with the onset of jaundice and that such impairment of carbohydrate function may or may not remain long in evidence, possibly no longer than a few days. It is also possible, occasionally, to obtain a positive test during the late and terminal phases of some cases of jaundice of chronic nature, such as cirrhosis of the liver or carcinoma of the head of the pancreas, in such instances, the test is rarely positive before hepatic cellular degeneration and disintegration have become so extensive that clinical and diagnostic studies have established the correct diagnosis. It may be repeated here that much of the failure of appreciation of this test stems from one of three sources: its use in suspected hepatic disease without jaundice, its use late in jaundice after carbohydrate functional efficiency has returned to normal test levels, or the failure to serialize the study during the course of jaundice in order to record the appearance and duration of the carbohydrate dysfunction and its disappearance.

Among other diagnostic procedures should be included a *flat plate of the abdomen* for the possible roentgenographic disclosure of opacities in the right upper quadrant. The occasional presence of a "silent stone" to which attention may thus be directed warrants the routine use of this measure. In addition, whenever possible, an *anti-body titer for Leptospira icterohaemorrhagiae and L. canicola*^{10, 11} should be obtained. While the appearance of a high titer is not to be expected in the early phase of the disease, such an initial reading serves as a base for later observation in patients whose persistent jaundice and clinical course may ultimately point toward Weil's disease, in earlier suspected cases, of course, the parasite may be demonstrable in blood smears.

2 Immediate Prognostic Studies

- (a) Prothrombin Time Determination
- (b) Total Serum Proteins and Albumin-Globulin Ratio Determinations
- (c) Determination of Blood Chlorides
- (d) Icterus Index Test
- (e) Methylene Blue Test
- (f) Quantitative Urobilinogen Test

(g) Determination of Serum Cholesterol Cholesterol Esters and Their Ratio

(h) Cephalin Cholesterol Flocculation Test.

Coinciding with the diagnostic studies to be performed initially are those procedures designed to determine the status of the patient along specific lines which may greatly influence the immediate prognosis and the administration of therapy. Particularly to be considered are the *determinations of prothrombin time, total serum proteins and albumin globulin ratio*, and, in instances of marked fluid loss by vomiting and/or diarrhea, *blood chloride estimations*. The notable tendency in liver disease toward diminution in the evolution and storage of vitamin K,^{12, 13} and the frequency of hypoproteinemia, especially reflected in the albumin fraction,¹⁴ are too well known to require elaboration.

This discussion seeks not to inquire into the mechanism of hypoprothrombinemia but rather to stress the importance of disclosing its presence in order to insure adequacy of corrective therapy as to both time and volume. Similarly, we need not attempt to dissociate the various possible components in the production of hypoproteinemia to appreciate the urgency for its relief although, in this instance, the source or sources of dysfunction, whether the failure of gastric protein digestion of small bowel assimilation or of hepatic metabolism, or the accelerated tissue activity, may influence the choice of the avenues and materials of correction. The early application of these studies is indicated, again, both for the prompt administration of specific therapeutic measures where needed, and for guidance in the interpretation of the same tests repeated serially during the course of the disease. Only by serialization of such studies can the value of treatment be recorded, the indication for continued or additional measures be appreciated or the late development of deficiencies be gauged. Undoubtedly such determinations go hand in hand with clinical observations, but, besides having confirmatory value, they frequently disclose early or minor aberrations prior to the development of grossly observable changes.

In milder cases these studies need be repeated only at seven to ten day intervals in more severe cases, the frequency must be governed by the composite clinical and laboratory picture. The late development, often insidious of abnormally low prothrombin and serum protein levels in long-continued cases of jaundice must be kept in mind, and the studies repeated until the clinical status of the patient, as well as his laboratory findings is completely reassuring.

The ascending, plateau and descending phases of acute hepatic disease may be observed by one or more of several methods. Probably the most widely used is the serialization of *icterus index determinations* at three to five day intervals or the similar use of the van den

Bergh reaction At this point the relatively new use of the *methylene blue test* again comes into prominence. Its simplicity and ease of performance render it available as a daily procedure where so indicated, and, pending further investigation, it appears capable of indicating a return to normal before blood bilirubin values have reached comparable levels, furthermore, in an appreciable percentage of instances, it has been observed to reascend to abnormal levels concurrently with the development of clinical relapse at a time when icterus index readings remained within the high normal range.⁵

Again, in the hands of other investigators, the *quantitative urobilinogen estimation* has given parallel results with a high degree of exactitude, but it lacks the ease and availability of the more gross methylene blue method. Still other workers follow these phases of jaundice of acute origin by serialization of *serum cholesterol-cholesterol ester determinations* in conjunction with the icterus index reading. During the period of increasing jaundice, demonstrated by a rising icterus index, the levels of serum cholesterol and cholesterol esters drop rapidly as a rule, the latter, at times, disappearing as the critical phase or plateau is reached, both elements may remain stationary for several days and then rise to normal levels as the icterus index begins to drop. Such a phenomenon is, of course, considered of good prognostic import. Again, however, considerations of economy of time, effort and materials come into play, and the decision as to the utilization of the test remains a matter of choice by the individual clinician.

It is well here to consider the *cephalin-cholesterol flocculation test* which has been very extensively used and, more recently, improved upon by the dark-room technic and advances in our knowledge of the preparation of reagents. Originally proposed for another purpose,¹⁶ its positive reaction in the presence of liver dysfunction was soon recognized^{10, 17} and its evaluation has been undertaken in many laboratories. The ensuing reports have varied in their degree of endorsement of its various fields of utility, chiefly because of the non-specificity of the reaction. As Wade and Richman¹⁸ stated with regard to its use in the diagnosis and observation of diffuse parenchymatous disease of the liver, "A negative reaction does not exclude one of these lesions. Similarly a positive flocculation cannot be interpreted as necessarily indicating liver dysfunction in the presence of other systemic disease." Although it may be readily employed, much as are the methylene blue, quantitative urobilinogen and other studies for such purposes, its delicacy in the detection of minor grades of liver dysfunction, such as that involved in malaria,^{19, 20} or in the remote prognosis of jaundice of acute origin may yet indicate an even more fertile field for investigation.

3 Remote Prognostic Studies

- (a) Bromsulfalein Test.
- (b) Hippuric Acid Synthesis Test.
- (c) Cephalin Cholesterol Flocculation Test

After jaundice of acute origin has largely subsided, as indicated by the return of blood bilirubin levels to normal or slightly elevated figures, the more remote aspects of prognosis come into prominence. While, once more, the clinical observation of the patient is of prime consideration, decisions involving the dietary requirements and contraindications, the length of continued rest, the possibility of relapse, and the long range outlook for chronicity, residual hepatic damage or eventual cirrhosis²¹ must be weighed by the laboratory methods at our disposal. The extent of these later disorders cannot be considered lightly by the clinician, the occurrence of cirrhotic changes after an apparently latent period, the tendency toward chronicity, and the potential danger engendered by impaired liver function in the presence of subsequent surgery or intercurrent infection have no invariable relationship to the severity of the original jaundice. As will be indicated in another report, these more remote developments are apparently the result of interaction of many factors including the prior nutritional status of the patient.

Admittedly the present means of assessing the presence and degree of residual liver dysfunction are not so satisfactory as might be desired. It appears well advised to continue the use of the icterus index and methylene blue tests once or twice weekly during the first several weeks of convalescence in order to permit detection of evidence of relapse and, whenever possible, initiation of therapy before clinical signs actually appear. Return of the icterus index to entirely normal levels is frequently long delayed because of gradual resorption and elimination of pigment from tissues in which it has been deposited, but any abrupt increase in its level often has the same significance as a recurring positive methylene blue test in pointing toward clinical or subclinical relapse. Only when these findings have leveled off and not until then, can the transition to the bromsulfalein hippuric acid and other tests be considered profitable.

Few such simple tests have undergone as many alterations and modifications of technic and interpretation as has the *bromsulfalein* test since the original work by Rosenthal and White²²⁻²³ on the impaired excretion of the phthaleins by the abnormal liver. The use of the 2 mg. per kilogram body weight dose by some and the 5 mg dose by others, the limitation of the 2 mg dose to jaundiced patients and the 5 mg to the nonjaundiced, the study of dye retention at various intervals of time and by several methods of fractionation all have served to make the interpretation of otherwise comparable series confusing and to cast doubt on the efficiency of the test. Much of

this difficulty is avoidable if the essential principle of the test and the accepted values for each modification be understood. The introduction of a liver-eliminated dye into the blood stream and the examination of a serum specimen after a specified interval for determination of uneliminated dye depends upon only three factors: the known normal values for such an interval, the degree of hepatic functional efficiency in regard to such elimination, and the status of the blood circulatory mechanism. Bernstein, Le Winn and Simkins²⁴ demonstrated in a substantial series that, among individuals who were free from known hepatobiliary disease, those persons with cardiac disorder in whom compensation was intact presented normal bromsulfalein readings, whereas in patients with concomitant pulmonary congestion a demonstrable degree of bromsulfalein retention was detectable; conversely, study is now complete but not reported indicating the influence of circulatory dysfunction on bromsulfalein retention in known hepatobiliary disease. In the vast majority of cases of jaundice of acute origin, however, these factors of possible circulatory impairment need not be seriously considered, the chief consideration becomes one of the choice of technic and the interpretation of results of that technic. As a purely practical matter, the use of the bromsulfalein test during the acute phase of jaundice is not justified, it presents no information that is not obtainable in more significant form by the studies previously detailed. In its proper sphere of utility, the problem is largely a matter of the test-load of the dye to be introduced, the time interval to be employed and the determination of normals for that test period. The former standard of normal retention amounting to less than 10 per cent of the dye thirty minutes after the introduction of a dose of 5 mg per kilogram body weight has been brought into question by the normal standards set up by Mateer and his co-workers^{17, 25} of total disappearance of the dye from the blood stream twenty minutes after the use of the 2 mg per kilogram dose, and forty-five minutes after the 5 mg per kilogram dose. Others use a serial technic with the 5 mg dose and feel that normal limits of retention are represented by 10 per cent at thirty minutes and 2 per cent at sixty minutes. These variations are not so widely divergent as to be significantly incompatible, and further extensive studies of normal individuals will undoubtedly clarify the situation.

In the *hippuric acid synthesis test*, the oral administration has largely given way to the intravenous technic of Quick,²⁶ in which 1.77 gm of sodium benzoate is used, but the interpretation of the normal values in the resulting excretion is not quite satisfactorily settled. In the hands of some, the accepted figures are 0.60 to 0.95 gm expressed in terms of benzoic acid excreted in the urine as hippuric acid, others²⁶ believe that any amount less than 0.70 gm constitutes evidence of deficiency.

in hepatic synthesis and still others believe that the lower limit of normal excretion should be held at 10 gm. The consensus of most investigations would seem to place this low level of normal function at approximately 0.70 gm.

For the purpose of estimation of residual damage, either the bromsulfalein or the hippuric acid synthesis test may be employed, with the former preponderantly the choice of most investigators, who agree with Teitelbaum, Curtis and Goldhamer²⁷ that "in the absence of jaundice, the bromsulfalein test is the most valuable test in determining the presence of parenchymatous liver injury."

In the light of present wide utilization, it is possible that the *cephalin cholesterol flocculation test* may come to play an important role in disclosing early or comparatively mild degrees of chronicity or damage in this phase. In the remote prognosis just as in the immediate prognosis, the choice of studies is equaled in value by a methodical program of serialization. Early after the subsidence of acute jaundice, such studies are indicated at intervals of one to two weeks in order to aid in the guidance of resumption of physical activity or the continuation of bed rest. Later during convalescence or chronicity, studies at intervals of one month or longer are sufficient, but they should be continued over a long period of time. No arbitrary time limit can be set up for every patient, it is probable that examination for a two year period will serve to indicate permanent return to normal hepatic function or to disclose the need for further observation in instances of chronicity or the development of late changes.

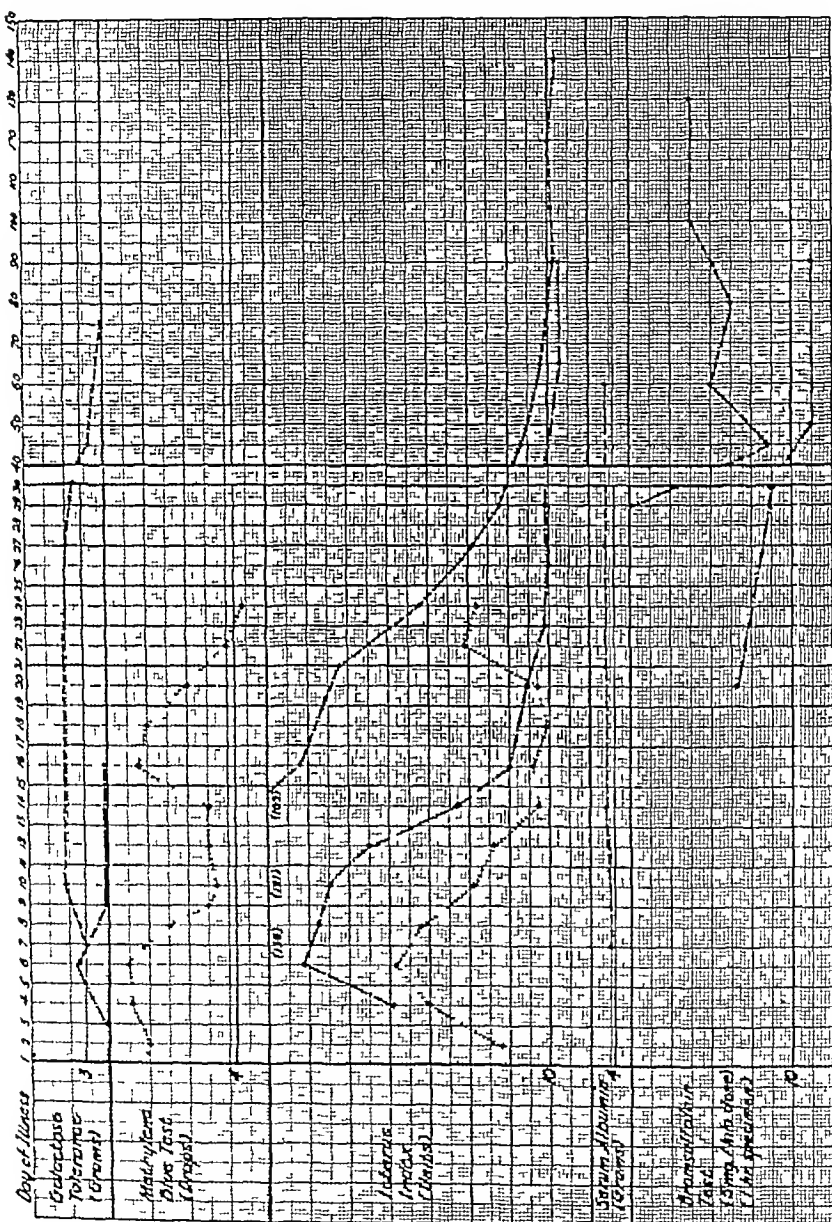
ILLUSTRATIVE CASE HISTORIES

Figure 175 will serve to illustrate some of the more salient features in the application of such a serialized system of study, as observed in three cases of acute infectious hepatitis chosen from an extensive series. In the cases here recorded many observations have been omitted in order to simplify the representation of the indication for, and the timing and significance of, a few essential readings.

CASE I.—S. B., a mess sergeant, 43 years of age, whose general appearance was that of a man of 55, had a long history of moderate addiction to alcohol. During the period of acute hepatitis the long-continued inadequacy of carbohydrate function, indicated by the elevation of the galactose tolerance findings, served as an early warning of the chronic hepatitis into which the patient ultimately drifted. When last observed, this man's apparently good clinical condition was not paralleled by his persistently abnormal bromsulfalein retention, a discrepancy which may assume large proportions in the presence of further hepatic disease or ensuing systemic infection or surgery.

CASE II.—W. C. This case illustrates the brief duration of impairment of carbohydrate function in certain cases, and emphasizes the need for prompt repetition of the galactose tolerance test at times. It is probable that a notable proportion of so-called "false-negatives" attributed to this test occur in just such instances,

the test having been performed prior to or subsequent to the peak of a moderate carbohydrate dysfunction. Other studies recorded for this patient illustrate the rapid return of hepatic function to normal levels, seen in the vast majority of mild cases of acute infectious hepatitis



Case B ----- Case WC. --- Case E L

Fig 175 - Graphic demonstration of brevity of carbohydrate dysfunction, prognostic significance of re-elevation of methylene blue test, and prolonged abnormality of bromsulphalein test in three illustrative cases (Note The notation '1 hr specimen' in connection with the bromsulphalein test should read "1/2 hour specimen")

CASE III - E L This case, which was under my observation for only a brief portion of the course, points up the value of the methylene blue test in revealing changes in the severity of hepatic involvement during the acute phase. In this

case the test served to indicate a relapse prior to any noteworthy change in either the clinical condition or the icterus index further findings of this test were observed to return to normal levels prior to a parallel shift in the icterus index or other studies

SUMMARY

Taken as a whole, it is readily seen that the foregoing observations offer nothing that has not been stated elsewhere by observers who have made detailed studies of liver function tests. However there appears with equal clarity, to be a need for elaboration as to the applicability of those studies particularly as regards their serialization and their use in specific situations in such a manner as to extract their maximum efficiency. Many may question the choice and evaluation of one or another of the studies suggested, or resent the omission of possibly valuable informative tests in this discussion. Particularly notable omissions have been the thymol turbidity²⁸ and the Harrison swab tests both of which are comparatively recent newcomers in development and extent of use. Either may ultimately assume a position of considerable importance or come to displace other studies now in standard use. The most recent observations by Recant, Chargaff and Hanger²⁹ suggest that the value of the thymol turbidity test may be heightened by its use as a complement to the cephalin cholesterol flocculation test, on the other hand, the preparation of the thymol reagent in a form suitable for varied climates or in varied forms which will give comparable readings is a minor obstacle to its more widespread trial at present.

The attempt here, however has been made simply to offer for consideration a three phase plan for the study of jaundice of acute origin and an evaluation of the applicability of those methods of study which today appear to possess the highest degree of efficiency, durability and readiness of performance. Such a choice is subject to differences of opinion which will continue to exist until more specific and more accurate liver function studies are devised. Nevertheless, in our present state of knowledge, much has been and can be gained in the diagnosis, prognosis and direction of therapy in jaundice of acute origin by the application in serial form of a systematic method of observation.

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